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THRESHOLDS OF CORTICAL REPRESENTATION

BY

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IN his writings on epilepsy, Hughlings Jackson often acknowledged his debt to Fritsch and Hitzig (1870), and especially to Ferrier, for their experimental stimulations of the cerebral cortex. One of Ferrier's (1873) professed objectives had been "to put to experimental proof the views entertained by Dr. Hughlings Jackson on the pathology of Epilepsy, Chorea and Hemiplegia, by imitating artificially the 'destroying' and 'discharging lesions' of disease, which his writings have defined and differentiated." The discharging lesion in epilepsy was paralleled in experiments in lower animals by "homologous convulsions" (Jackson, 1873*a*) which were brought on by "electrization" of certain parts of the brain's surface.

Hughlings Jackson (1874) believed that "the value of Ferrier's researches as contributions to the anatomy and physiology of the nervous system could scarcely be over-rated." They extended to the monkey and other animals the observations of Fritsch and Hitzig on cerebral localization in the dog. The areas defined experimentally "have no exact line of demarcation from each other and where they adjoin, stimulation is apt to produce conjointly the effect peculiar to each" (Ferrier, 1876). This might be due to spread of stimulus: "the areas overlap each other . . . if the currents are too strong" (Ferrier, 1875). He believed that the underlying localizations were absolutely discrete (Ferrier, 1890).

In one respect the results of Ferrier and of subsequent workers did not show complete accord with the clinical observations of Jackson, about which he was so often emphatic. In epilepsy, the Jacksonian march started as a rule in certain parts of the body, as though there might be seats of election for the onset of convulsions (Jackson, 1873*b*, *c*). "There are three parts where fits . . . mostly begin, (1) in the hand, (2) in the face or tongue or both, (3) in the foot. . . . When the fit begins in the hand, the index finger and thumb are usually the digits first seized: when in the face, the side of the cheek is first in spasm: when in the foot almost in-

variably the great toe." Ferrier (1873) had in fact obtained some results bearing on this question. But his results do not appear to have attracted attention then or subsequently. " Simultaneous diffused irritation of the whole of the centres was induced by causing the current to traverse the hemisphere from end to end. . . . In the rabbit the convulsions usually begin in the mouth and lips, and in the cat the eyelids and face first, next the shoulder and paw, and lastly the hind-leg and tail were thrown successively into convulsions. Here we observe the muscles most in voluntary action are the first to be attacked. The centres for these . . . are more excitable and more easily discharged. . . . Hence a general irritation of the whole hemisphere manifests itself primarily in the more excitable parts, and these coincide with the most voluntary centres." Ferrier had not then extended his work to monkeys. In that same year, Jackson (1873*c*) remarked : " It is very interesting to me to find that Ferrier's independent researches confirm the general principle. . . . " And in speculating on Ferrier's research, he had been curious to know what would be the results in the monkey. " Among the fits which *begin unilaterally*, the commonest are those in which the spasm starts in the index-finger and thumb. . . . The thumb and index-fingers are the most voluntary or specialized parts of the body. . . . The thumb in man has a distinct flexor longus pollicis. The thumb in monkey is less specialized than in man. If, then, we discover in a monkey the homologue of the part discharged in my patient, we shall expect from its discharge a fit of less special kind ; for example, not a fit beginning in its pollex, but more likely one beginning in the whole of its five comparatively little differentiated digits at once, if not in the whole arm " (Jackson, 1873*d*). He next mentioned an unpublished case of fits beginning in the left great toe : " Here, again, I await Dr. Ferrier's further researches in comparative physiology of the convolutions."

But interest in differential thresholds does not seem to have been sustained. Ferrier did not discuss it further, and Schäfer (1900) makes no mention of it in his textbook. Instead attention is focused on the order of representation of parts of the body and on the order of their involvement in the march of an attack. Belief in restricted localization gained ground so that in 1888 Mills was found to write enthusiastically : " Wonderful indeed is this motor zone of the cerebrum, a marvellous mosaic of centres of function . . . a mosaic to each block, angle and jointure of which the neurologist can point the surgeon and say : ' cut here or there, or touch not this or that ' " (Mills, 1888). Schäfer too seems to have been a believer in narrow localization, though he pointed out (1887) that fissures near the " motor " area do not serve as exact boundaries of that area. In commenting on the account of Beevor and Horsley (1887, 1888) of thumb movements from a rather larger cortical area (Macaque) than was then generally recognized, Schäfer (1900) wrote in his textbook, " there must have been some unrecognized source of error in this observation." These authors had also reported : " the hallux

is frequently represented all over the area for the movements for the lower limb."

As experience accumulated with the passage of years, it became clear at any rate that motor localization, investigated by using artificial stimuli, bore no fixed relationship to the minor cerebral landmarks which themselves varied unsystematically from species to species and from individual to individual. It was definitely abandoned by Leyton and Sherrington (1917) in their study of the chimpanzee, orang-utang and gorilla, using brief near-threshold faradic stimuli. " We had supposed at the commencement of our experiments " (which of course began at the beginning of the century, Grünbaum and Sherrington, 1901) " that the identification of exactly corresponding points in the two hemispheres of an individual and in the hemispheres of different individuals could be much more nearly possible than our experience has left us with the impression that in fact it is. The dissimilarity of the convolutional pattern of the hemispheres even in individuals of the same species . . . and the seemingly variable relation of analogous functional points to sulci of corresponding name, makes it practically impossible to decide with sufficient exactitude what point on the hemisphere of one individual is identical with a given point upon another hemisphere." They listed 445 primary movements, many closely similar to one another, but not all elicitable from the same individual or the same anthropoid species. They remark on the large area of representation of the tongue : that " retraction of contralateral angle of the mouth, either primary or secondary, seemed the most common of all lip movements ": the existence of separate primary representation of thumb and of index : " the fields for primary movements of this digit appeared in some of our specimens to be larger even than that for the thumb." Their fig. 9A is reproduced here (fig. 1). We have marked appropriate points to show the extent of the fields from which in a gorilla primary or secondary movements of hallux, thumb, tongue and angle of mouth were obtained, with or without other movements. By facilitation, in another experiment, " primary movements of thumb and index were obtained from below upwards, as far as the shoulder field, involving a not inconsiderable fraction of the whole arm area." In this classic study, emphasis moves away from anatomical localization in the cortex to fragmentary movements of limb parts and to instability of function as shown by facilitation and reversal (Graham Brown and Sherrington, 1912 ; Graham Brown, 1916).

Foerster (1936) mentions similar instability in the motor cortex of man. Applying galvanic stimulation at one-second intervals he found that " the so-called thumb focus is not an absolute focus ; it contains elements representing the thumb, the fingers and the hand, intermixed with each other. The elements of the thumb are numerically far superior to the other elements and they have the lowest threshold ; therefore they are the first to respond to stimulation of the focus .. . . The foci of the different

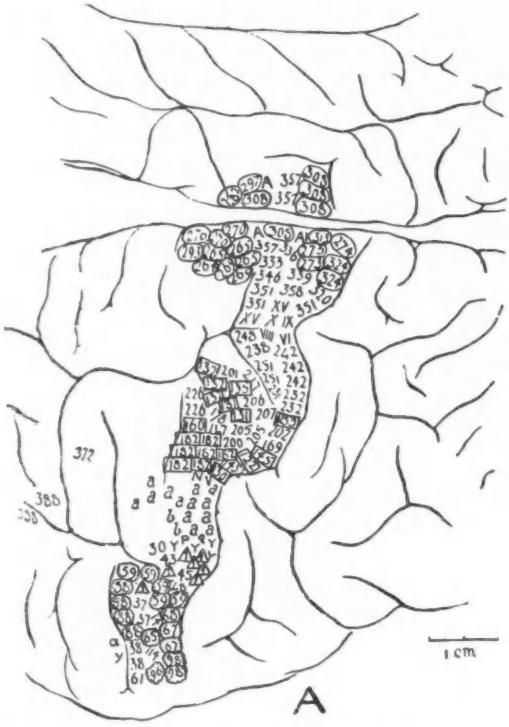


FIG. 1.—"*Gorilla* 1," Leyton and Sherrington, 1917. Left Rolandic region showing extent of representation of hallux, thumb, angle of mouth and tongue. Points yielding movements of those parts, primarily or secondarily, alone or with other movements, are indicated thus: Ovals—hallux. Oblongs—thumb. Triangles—angle of mouth. Crenated circles—tongue. Each number refers to a specific movement or combination of movements. Note that the same number may appear at several points, e.g. 182 ("All fingers and thumb flexed" (first movement); "wrist flexed" (second movement)).

parts of the body are not like the stones of the mosaic to which they were compared, but they overlap to a more or less considerable degree."

It is to be remembered that the technical methods available for use in experiments to earlier workers were limited. General anæsthetics needed throughout the experiment depress nerve tissue, especially at synapses. Moreover choice of them was limited. Electrical methods of stimulation were not very varied, and, as so often with electricity, were capricious in action. Stimulation by electricity of cells lying among the complex layers of cortical tissue is especially difficult, because uncertain, and has not, even yet, been accomplished to perfection. Electrodes have been too large, nerve units too deep. All the time of the experiment anæsthetic depression may vary and induce variation in response. Blood supply

may alter. Writing of these difficulties, Sherrington (1906) commented thus : " Although it is not surprising that such territorial subdivision of function should exist in the cerebral cortex, it is surprising that by our relatively imperfect artifices for stimulation we should be able to obtain clear evidence thereof."

Galvanic and faradic stimulation were the methods of choice of earlier workers. Fritsch and Hitzig (1870) employed chiefly the former, Ferrier and his successors chiefly the latter. Ferrier (1876) considered faradic stimulation superior to galvanic because a larger range of movements could be evoked, and electrolytic injury was avoided. Foerster (1936) A recent writer (Hines, 1944) using 60 c.p.s. alternating current has been aware of the limitations of artificial stimulation. " Electrical stimulation of the surface of the pre-central motor cortex is at best a crude method of gaining knowledge of its contribution to function." Again : " The type and depth of anæsthesia determines within limits the corticofugal system aroused, as well as the spontaneous activity of the cortex itself." Significantly Penfield and Boldrey (1937) said of their well-known observations on the unanæsthetized human cortex, " Our results from stimulation resemble those of Grünbaum and Sherrington (1901) in the chimpanzee except that they got no response from the post-central gyrus." (Beevor and Horsley (1887, 1888) did in the macaque.) " This may be due to a difference in man and anthropoid or more likely it is due to light anæsthesia which it was necessary for them to use during the stimulation."

In quite recent times, new possibilities of electrical stimulation have emerged by the introduction of electronic stimulators delivering pulses of current independently variable in shape, duration, strength and frequency of repetition. The use of such instruments already tends to reveal a less rigid plan of motor representation than was sometimes inferred from classical experiments. Thus Fulton (1949) and Livingston (1949) quote examples of cortical points which yield different motor results depending on the parameters of stimulation employed. Fulton observes : " These considerations make it clear that much of the earlier work on stimulation of the cortex with faradic currents, usually of unrecorded frequency, should be re-examined under more carefully controlled conditions."

Liddell and Phillips (1950) have used a " square wave " stimulator which allows a wide choice of strength, frequency and duration of stimulating current pulses. Combined with it they have used mechanically applied electrodes, which enable accurate placing to be achieved and maintained. François-Franck (1887) was one of the earliest to employ this rarely used device. Electrode positions are marked on a photograph of the individual cortex as investigation proceeds. Liddell and Phillips also used hexobarbitone for anæsthetic, which is less depressing than some in customary use. Under these conditions of experiment, they have lately shown that the areas of representation of various movements in

the motor cortex of the baboon can be made to vary in size according to the parameters of stimulation and the level of narcosis. Single pulses (optimum duration 5 msec.) find the cortex in a quiescent unfacilitated state and elicit movements confined to distal segments of the limbs and the face. The actual movements vary a little from one preparation to another: the maps of their representations show boundaries which fluctuate with strength of stimulation and grade of narcosis. The lowest-threshold region is located in the middle third of the precentral gyrus which, with single pulses (1–1·6 mA.) yields flick-like movements of the opposite thumb, index and little finger, but no movements from other parts of the cortex, or of other parts of the body. With stronger pulses, the thumb-index-minimus field expands medialward and the medial part of the motor gyrus now responds, giving flick movements of the opposite hallux, either alone or with one or more of the other toes. At about the same strength, or a little more, the lateral part of the precentral gyrus yields flicks of the tongue, or opposite angle of the mouth, or of both together. The threshold is always lowest for the "thumb complex," usually higher for the "toe complex," and highest for the "face complex," though in one experiment tongue and toe had the same threshold (figs. 2–7). When the anæsthetic is deep, no response is

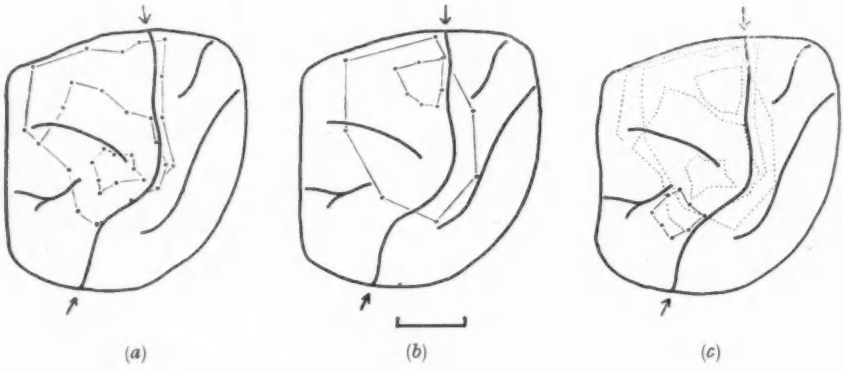


FIG. 2.—*Papio papio*, ♀, 5 Kg. Left Rolandic region, stimulated with single pulses 4·5 msec. in duration. Scale 10 mm. Arrows mark the central fissure. (Traced from the photographic map.) (*a*) Extent of thumb-index-minimus area at strengths 1·2 mA., 1·6 mA. and 2·7 mA. (*b*) Extent of hallux-middle toe area at strengths 2·05 mA. and 4·7 mA. (*c*) Area for angle of mouth (solid line) at strength 2·35 mA. Thumb and toe areas indicated by dotted lines.

obtained with 1–5 mA., but as the anæsthetic lightens, the "thumb complex" is first to respond. With stronger shocks and light narcosis, the three areas overlap so widely that each shock causes flick-movements simultaneously in all three peripheries from the greater part of the

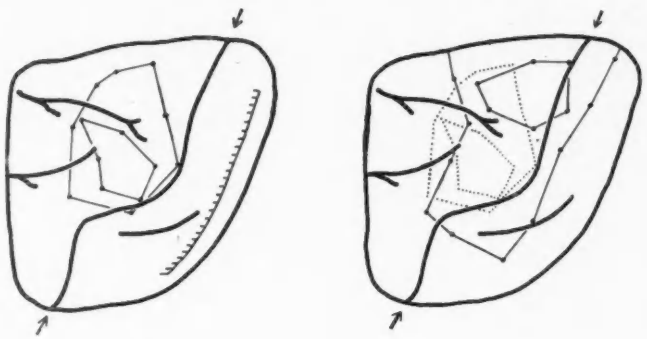


FIG. 3.—*Papio papio*, ♂, 4·2 Kg. Left Rolandic region. Single 4·5 msec. pulses. Arrows mark central fissure. Scale in mm. (Traced from the photographic map.) (*a*) Extent of thumb-minimus area, 1·4 and 2·35 mA. (*b*) Extent of hallux area, 2·35 and 2·7 mA. (solid line). Threshold for tongue and angle of mouth (not mapped) 3·7 mA.

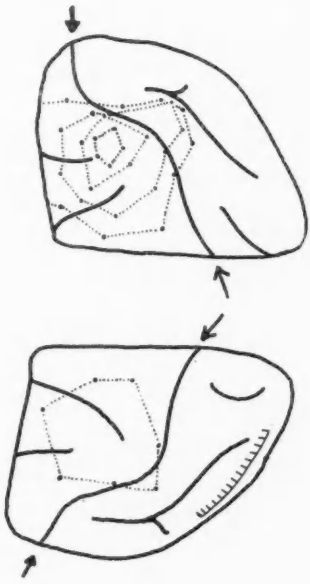
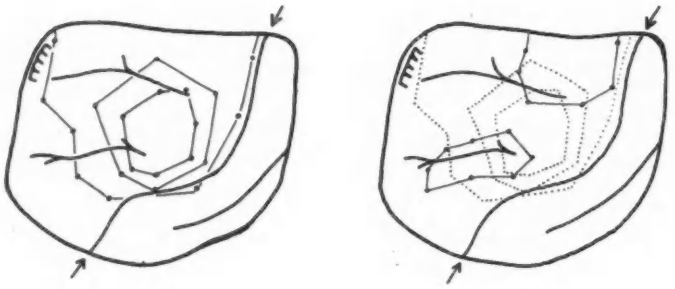


FIG. 4.—*Papio papio*, ♀, 4·0 Kg. Both Rolandic regions (anterior borders at left-hand edge of figure). Single 4·5 msec. pulses. Arrows mark central fissures. Scale in mm. (Traced from the photographic map.) *Right hemisphere :* (above) extent of thumb-minimus area, 1·6, 1·8, 1·9 and 2·35 mA. *Left hemisphere :* (below) corresponding area at strength 1·9 mA.

motor area. These stronger shocks when applied in the centre of the "thumb complex" field generally evoke movements of the wrist and elbow as well, but no other movements (Liddell and Phillips, 1950).

If a frequency of stimulation of say 50 c.p.s. instead of single stimuli be applied at the same strength, the simple large-scale map of distal parts changes dramatically into the classical map of finer grain in which



(*a*) (*b*)

FIG. 5.—*Papio papio*, ♂, 6·0 Kg. Left Rolandic region. Single 4·5 msec. pulses. Arrows mark central fissure. Scale in mm. (Traced from the photographic map.) (*a*) Extent of thumb-index-minimus area, 1·0, 1·2 and 2·05 mA. (*b*) Extent of hallux-toes area (medial, solid line) and tongue (lateral, solid line), 1·6 mA.

movements of all parts of the body are represented. In fig. 8 is presented such a map for comparison with the "single-pulse" map of the same cortex (fig. 7A, B). 91 points were stimulated in random sequence (*see* table). A minimal interval of thirty seconds elapsed between each stimulation. 21 points were stimulated more than once. If there was no response after five seconds, stimulation was discontinued. On only six occasions were clonic after-discharges seen and they were invariably focal.

In fig. 8 the area of lowest threshold for the "thumb complex" with single pulses (1·4 mA.) is enclosed with a black line. The area, so stimulated, was the only region of the cortex to yield any visible movement, which was of the first dorsal interosseous region, with palpable contractions and action potentials in the underlying muscle. With the same current pulses at 50 c.p.s., 71 out of 91 points now yielded movements. The 11 points inside the black line (fig. 8) now gave the differentiated movements catalogued in the table, without detectable delay in their onset, except on the fringe of the area (points 45, 57 and 74). In the leg area of fig. 8 points 6, 12, 14 : in the arm area points 34, 37, 38, 39, 46, 49, 51, 60, 66, 73 : in the face area points 77, 78, 79, 83 and 84 were the only others from which similarly prompt movements, delayed by less than one second, were obtained. These points were located within the areas of lowest threshold for foot, hand and face which are shown in the single pulse map

(fig. 7). The remaining points, outside these areas, needed summation periods (as defined by Cooper and Denny Brown, 1927) of up to five seconds, the arbitrary maximum which was set to the stimulation period. These responses at higher frequencies are not altered by reducing the pulse-duration to 1·0 msec. or 0·4 msec. Some points were re-stimulated with stronger pulses, as noted in the table.

Of the 21 points that were re-stimulated, 15 gave somewhat different movements on different occasions. For example, point 88, when first excited, caused curling of the tongue followed by closure of the jaw, but when explored again, about one and a half hours later, gave protrusion of the tongue towards the stimulated side. Such instability is well recognized.

At the higher frequency of stimulation, as the data in the table show, much more cortical tissue is awake and discharging. The simple pattern of figs. 2–7 is overlaid by congeries of newly activated neurones and grows into the classical cortical map with its partitioned topography. As frequency of stimulation increases at any point, proximal joints become involved, and the summation period shortens. The character of this response of proximal joints—variable latency ending in a rapid burst of action—recalls the crossed extensor reflex and is quite different from the rapid little flicks previously seen at the periphery.

How many of the results in the Table are due to genuine cortical instability cannot be decided until technique is so improved that single cortical units can be stimulated. The passage of an electric current, even near threshold, through three dimensions of a moist mosaic must be sufficiently variable to give an impression of instability. Nevertheless the maps now presented show how different types of response can be called up, by different frequencies of stimulation, from one and the same motor area.

The thumb-index-minimus muscles can be activated from a much wider cortical area than experimentalists have usually supposed ; and the area's wideness is shown most easily when the frequency of stimulation is low. For the hallux, these conditions may not need to be quite so rigidly observed. Indeed the very wide area for the hallux shown by Beevor and Horsley (1888) and for the thumb (Beevor and Horsley, 1887), which result Schäfer (1900) doubted, shows that these earlier workers were not far from making the observations which are now recorded.

Walshe (1943) has remarked on the common onset of focal epilepsy in thumb, face or toes in relation to the coarse lesions or the diffuse pathological states of the cortex which may predetermine it. He emphasizes that the thumb, face and toes must be widely represented in the cortex : " it is impossible to suppose that pathological lesions in the cortex have some special affinity for the thumb-index, angle of mouth and great toe

'areas.'" Our experiments invite the speculation that the frequency of pathological discharge may be important in determining which parts are first affected. If the frequency were low enough, movements of these very parts might be expected wherever the focus, within wide limits, is located. Walshe (1943) has also observed that a fit confined throughout to the parts first moved is "a relatively leisurely clonus of moderate intensity . . . it has neither the rapidity of ryhthm nor the intensity of convulsion that occurs in these muscles when the convulsion spreads up the limb."

Conclusion

Hughlings Jackson and subsequent clinical observers have often called attention to the frequent early involvement of the thumb-index, mouth and hallux in convulsive discharges from the cerebral cortex. But the cortical motor areas, as delineated in the early days of electrical stimulation in animals and projected on to the human map by inference, appeared as restricted piecemeal portrayals of the body's musculature. How then to explain the existence of special areas and their "overfunction" as seats of election in focal epilepsy ? This difficulty now seems capable of explanation by critical reassessment of some earlier work and by the results which we now describe. The earlier experimentalists in the main directed their attention rather to anatomical localization than to differences between the thresholds of loci. Interest in anatomical localization led to the "mosaic" hypothesis, which held sway till the experiments of Leyton and Sherrington. The doubts which they expressed have been confirmed by the more recent observations of Glees and Cole (1950), who have followed motor recovery after small lesions in the macaque. If the "mosaic" hypothesis is true and absolute, there should be no recovery in the arm when the "arm-area" is excised. But it is well recognized that recovery does occur, due apparently to the emergent functioning of cortical fields surrounding the classical area which has undergone excision.

We have recently described how extensive areas for thumb-index, hallux and face declare themselves when stimuli are weak single "square-waves." In the present communication, we trace the change in one and the same cortex of a baboon from the map of few effects and extensive areas delineated by single shocks to the map of many effects and narrow areas delineated by repetitive stimulation, e.g. 50 c.p.s. The latter grows into the traditional map of "motor points." Thus our evidence accords precisely with the prophetic writing of Walshe : "It is suggested that Jacksonian fits have their characteristic form of onset because the movements concerned are those that have the widest fields of low threshold excitability." The experiments which we have described support the belief in the wide fields of low excitability for the thumb-index, hallux and face.

Point	*Order in which stimulated*	*Time*	*Minutes since last injection*	*Response*	*After discharge*	*Latency*
1	19	2015	27	Flexion knee and hip	0	2·5″
	108	2308	11	(2·7 mA.) Flexion knee and hip	+	Immediate
2	13	2011	23	Nil	0	—
	115	2320	23	(2·7 mA.) Flexion toes, dorsiflexion ankle, flex-knee and hip	0	Immediate
3	12	2010·5	22·5	Flexion little toe, plantar flexion ankle	0	3·5″
4	11	2010	22	Flexion little toe, inversion foot	0	2·5″
5	9	2008	20	Nil	0	—
6	8	2007·5	19·5	Flexion toes, plantar flexion ankle, inversion foot	0	Immediate
	116	2321	24	(2·7 mA.) Flexion toes, plantar flexion ankle, inversion foot	+	,,
7	7	2007	19	Inversion of foot	0	5″
8	18	2014·5	26·5	Nil	0	—
9	17	2014	26	Flexion knee and hip	0	2·5″
10	16	2013	25	Flexion knee and hip	0	1·5″
11	15	2012·5	24·5	Flexion knee and hip	0	1·5″
12	23	2017	29	Inversion of foot	0	2″
	100	2241·5	65·5	Flexion hip and knee, dorsiflexion of ankle	0	Immediate
13	10	2009	21	Flexion little toe, inversion foot	0	Immediate
	49	2044	9	Flexion little toe, inversion foot	0	0·5″
14	2	2003	15	Flexion little toe, then other toes	0	1·5″
	103	2245·5	69·5	Extension toes, dorsiflexion ankle inversion foot, then flexion toes	0	Immediate
	104	2249	73	(1·4 mA., 1 msec.) Extension toe, inversion foot, then flexion toes	0	0·5″
15	1	2002	14	Nil	0	—
16	20	2015·5	20	Nil	0	—
17	14	2012	24	Flexion knee, hip, ankle	0	1·5″
18	21	2016	28	Nil	0	—
19	22	2016·5	28·5	Inversion foot	0	4·5″
20	24	2017·5	29·5	Inversion foot	0	5″
21	27	2020	32	Flexion hip	0	2·5″
22	3	2004	16	Flexion toes, dorsiflexion ankle	0	2·5″
23	67	2100	25	Nil	0	—
24	52	2047	12	Extension fingers, radial deviation wrist	0	3·5″

Point	*Order in which stimulated*	*Time*	*Minutes since last injection*	*Response*	*After discharge*	*Latency*
25	53	2047·5	12·5	Spreading and extension fingers	0	1·5″
26	25	2018	30	Nil	0	—
	96	2237	61	Nil	0	—
27	26	2019	31	Extension elbow, flexion hip	0	2″
28	58	2051	16	Retraction shoulder	0	2·5″
29	28	2020·5	32·5	Extension elbow	0	1·5″
30	4	2005	17	Adduction shoulder, flexion toes	0	1·5″
31	5	2005·5	17·5	Nil	0	—
32	51	2046	11	Pronation, adduction of fingers	0	2·5″
33	50	2045	10	Adduction and extension of fingers	0	1·5″
34	63	2055·5	20·5	Radial deviation of fingers 3, 4, 5	+	5″
	99	2241	65	Flexion elbow	0	Immediate
35	59	2052·5	17·5	Extension fingers	0	2″
36	54	2048	13	Adduction and radial deviation fingers	0	Immediate
37	65	2058	23	Ulnar deviation and extension fingers 3, 4, 5	0	0·5″
	110	2311	14	(2·7 mA.) Pronation, extension wrist, extension toes, inversion foot	0	Immediate
38	60	2054	19	Retraction shoulder	0	1″
	112	2315	18	(2·7 mA.) Extension elbow, pronation, flexion toes	0	Immediate
39	30	2021·5	33·5	Extension elbow, retraction shoulder	0	0·5″
40	6	2006	18	Retraction shoulder, pronation forearm	0	1·5″
41	68	2101	26	Nil	0	—
42	72	2105	30	Abduction index, radial deviation fingers 3, 4, 5	0	2·5″
	111	2312	15	(2·7 mA.) Radial deviation wrist, extension fingers, flexion elbow, lower lip, extension little toe	0	Immediate
43	56	2050	15	Abduction index, extension other fingers	0	Immediate
44	55	2049	14	Abduction index, extension other fingers	0	Immediate
45	66	2059	24	Adduction and extension fingers 3, 4, 5 pronation	0	0·5″
46	62	2055	20	Pronation, ulnar deviation hand	0	0·5″

Point	*Order in which stimulated*	*Time*	*Minutes since last injection*	*Response*	*After discharge*	*Latency*
47	29	2021	33	Nil	0	—
48	71	2104	29	Nil	0	—
49	46	2034	46	Flexion elbow	0	0·5″
	47	2042	7	Nil	0	—
50	45	2032·5	44·5	Flexion elbow	0	1·5″
51	44	2032	44	Retraction shoulder. Flexion elbow	0	0·5″
	48	2043	8	Abduction index	+	4″
52	70	2103	28	Adduction thumb and minimus, extension other fingers	0	Immediate
53	57	2050·5	15·5	Adduction thumb, extension fingers	0	Immediate
54	31	2022	34	Retraction shoulder pronation	0	4″
55	73	2105·5	30·5	Upper lip	0	1·5″
56	41	2030	42	Angle of mouth, supination, extension elbow	0	1·5″
57	43	2031	43	Retraction shoulder, flexion fingers	0	0·5″
58	61	2054·5	19·5	Flexion thumb, adduction fingers	0	Immediate
59	69	2102	27	Adduction thumb and minimus, extension other fingers	0	Immediate
60	32	2022·5	34·5	Dorsiflexion wrist, pronation	0	0·5″
61	95	2130	11·5	Nil	0	—
62	94	2130	11	Angle of mouth, flexion fingers, supination	0	1·5″
	105	2255	79	(2·7 mA., 4·5 msec.) Angle of mouth, adduction thumb	0	Immediate
	106	2256	80	(2·7 mA., 1 msec.) Angle of mouth and tongue, adduction thumb, flexion elbow	0	Immediate
	107	2306	9	(2·7 mA., 4·5 msec.) Flexion thumb and index, ulnar flexion wrist, upper lip	0	Immediate
63	40	2029	41	Upper lip, flexion thumb and wrist, and supination	0	1·5″
	97	2238	62	Upper lip, flexion wrist, supination, flexion fingers	0	1·5″
	113	2316	19	(2·7 mA.) Flexion fingers and thumb, supination, upper lip	0	Immediate

Point	*Order in which stimulated*	*Time*	*Minutes since last injection*	*Response*	*After discharge*	*Latency*
64	42	2030·5	42·5	Flexion thumb, flexion then extension fingers, extension elbow	0	1·5″
65	64	2056·5	21·5	Flexion thumb, abduction index, adduction other fingers	0	Immediate
66	33	2023	35	Flexion wrist, extension fingers	0	0·5″
	102	2245	69	Pronation, ulnar deviation and extension fingers 3, 4, 5	0	Immediate
67	82	2113	38	Nil	0	—
	114	2319	22	(2·7 mA.) Nil	0	—
68	74	2106	31	Flexion elbow, angle of mouth, withdrawal tongue	0	1·5″
69	93	2129	10	Angle of mouth, withdrawal tongue, flexion and adduction fingers 3, 4, 5	0	2″
70	39	2027	39	Supination, flexion thumb and fingers, angle of mouth and withdrawal tongue	0	2·5″
71	38	2026·5	38·5	Flexion thumb, fingers and wrist	0	2″
72	37	2026	38	Flexion thumb, fingers wrist	0	1·5″
73	36	2025·5	37·5	Flexion thumb, fingers, wrist	0	0·5″
74	35	2025	37	Flexion thumb and fingers	0	0·5″
75	34	2024	36	Nil	0	—
76	92	2128	9	Withdrawal tongue, angle of mouth	0	1·5″
77	77	2109	34	Withdrawal tongue	0	0·5″
78	91	2127	8	Withdrawal tongue, angle of mouth	0	1·5″
	98	2239	63	Withdrawal tongue, angle of mouth, extension and adduction thumb	+ (Tongue and face only)	0·5″
79	75	2106·5	31·5	Tongue, angle of mouth	0	0·5″
80	76	2107	32	Nil	0	—
81	87	2117	42	Nil	0	—
82	90	2126	7	Withdrawal tongue	0	4″
83	88	2123	4	Withdrawal tongue, angle of mouth	0	0·5″

Point	*Order in which stimulated*	*Time*	*Minutes since last injection*	*Response*	*After discharge*	*Latency*
84	78	2110	35	Withdrawal tongue	0	0·5″
	109	2310	13	(2·7 mA.) Withdrawal tongue, angle of mouth, extension thumb	+ (Mouth and tongue only)	Immediate
85	80	2111	36	Nil	0	—
86	86	2116	41	Withdrawal tongue	0	2″
	89	2124	5	Tongue protruded to left, then jaw closed	0	2·5″
87	79	2110·5	35·5	Tip of tongue curled	0	1·5″
88	81	2112	37	Tongue curled, jaw closed	0	1·5″
	101	2243	67	Tongue protruded to left	0	3·5″
89	85	2115·5	40·5	Nil	0	—
90	83	2114	39	Tongue protruded to left, jaw closed	0	1·5″
91	84	2115	40	Nil	0	—

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LEGENDS FOR PLATES II AND III

FIG. 6.—*Papio papio*, ♂, 12·25 Kg. Left Rolandic region. 4·5 msec. pulses. Arrows mark central fissure. Scale in mm. (*a*) Dotted line : thumb-index-minimus area, strength 1 mA. Continuous line : thumb-index-minimus area (medial), strength 1·4 mA. Tongue area (lateral), strength 1·4 mA. (*b*) Continuous line : Hallux area (medial), thumb-index-minimus area (middle), tongue area (lateral)—strength 2·7 mA. Dotted lines show positions of areas figured in 6 (*a*).

FIG. 7.—*Papio papio*, ♀, 4·0 Kg. Left Rolandic region. 4·5 msec. pulses. Arrows mark central fissure. Scale in mm. (*a*) Dotted line : thumb-index-minimus area, 1·4 mA. Solid circles and solid line : thumb-complex, open circles and solid line : hallux and toes, 2·35 mA. (*b*) Solid circles : thumb-complex, 2·7 mA. Open circles : toe complex, squares : tongue, 2·7 mA. Triangles : angle of mouth, 2·7 mA. Dotted lines enclose areas of lowest threshold for thumb and toe complexes, as shown in fig. 7(*a*).

FIG. 8.—The motor area shown in Fig. 7(*a*) and (*b*) was stimulated by 4·5 msec. pulses of strength 1·4 or 2·7 mA., but delivered at 50 c.p.s. instead of singly. The responses obtained from each numbered point are listed in the table. Solid line : smallest extent of thumb-index-minimus complex with single 1·4 mA. pulses (*see* fig. 7(*a*)). The " arm " and " leg " areas are separated by a line joining points 1–9–10–17–19–20–27–30. " Arm " area reaches down to line 68–69–70, and overlaps upper border of " face " area, line 68–55–56–63–70. Further details in table and in text. Arrows mark central fissure. Scale in mm. Point 55 is the unnumbered point in front of point 56.

PLATE II

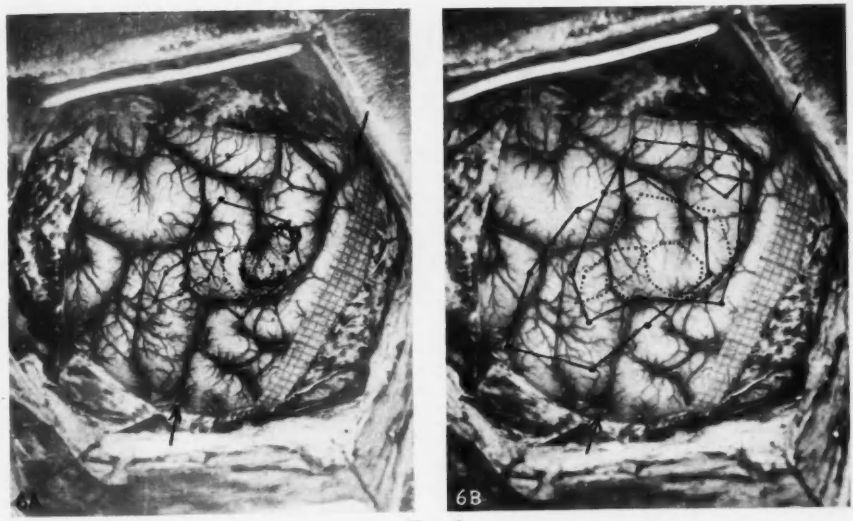

FIG. 6

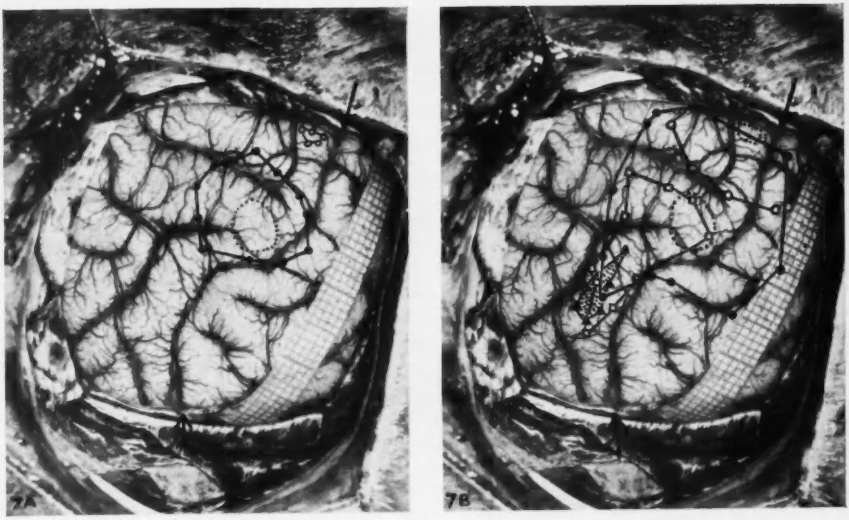

FIG. 7

To illustrate article by E. G. T. Liddell and C. G. Phillips.

PLATE III

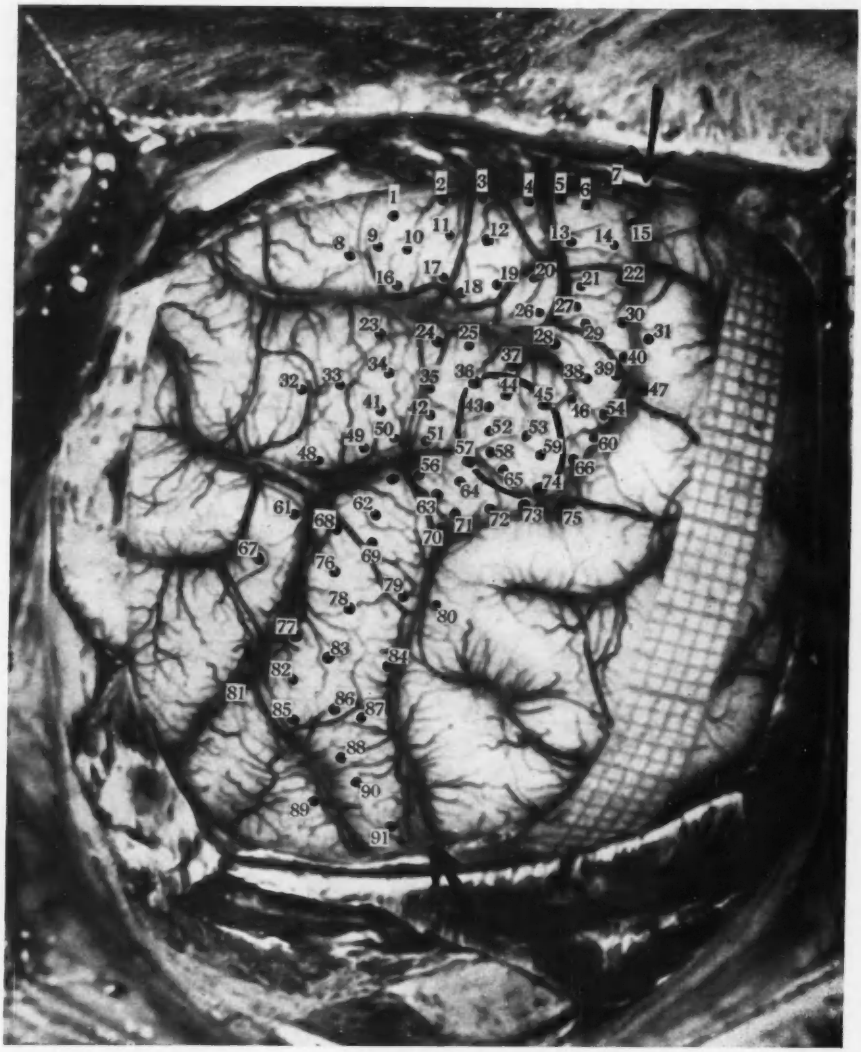

FIG. 8

To illustrate article by E. G. T. Liddell and C. G Phillips.

ENCEPHALITIS AND ENCEPHALOMYELITIS IN ENGLAND AND WALES DURING THE LAST DECADE*

BY

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THE work on which this survey is based was begun in the autumn of 1941, but it is convenient to include the two previous years, and to commence at the outbreak of war in September 1939. During this decade encephalitis has been rare in England, but in addition to those types which were well recognized during the preceding twenty years, a few cases have been reported or personally observed of two acute and two subacute forms which had not been recognized previously as occurring in this country. In addition cases of toxoplasmosis in some of which the brain has been involved have recently been reported, but these are not covered by the present survey which deals only with forms of encephalitis which are presumed to be either directly or indirectly due to virus infection.

In the autumn of 1941 the late Professor James McIntosh and the writer were asked by the Ministry of Health to examine material from fatal cases which were presumed to be of encephalitic character. One reason for this investigation was the fear, fortunately unfounded, that under war conditions some of the insect-borne types which had caused epidemics in the U.S.A. and the Far East might be brought to this country. Professor McIntosh, who undertook the animal inoculations had the help of Dr. F. R. Selbie in this work, while the writer was chiefly responsible for the histological examinations. The final diagnosis was reported to the Ministry after discussion by the members of the team.

In addition to the material submitted through the Ministry the writer encountered during his routine work, or was sent by pathologists in different parts of the country, material from cases of various kinds. The material examined during the war years has been the subject of a short report for the " Medical History of the War " by the three members of the team, but certain cases which were of special interest have been more fully reported in this survey.

As the Ministry of Health is not responsible for Scotland and as none of our material came from there, the survey has been restricted to England and Wales.

In his report for the years 1940–45 the Registrar-General for England and Wales has been at some pains to verify the incidence and mortality of acute encephalitis other than that following vaccination, measles and other infectious illnesses. He calculated that acute cases had fallen during those years from about 200 to less than 100 per annum with a

*An amplified form of the second part of the Hughlings Jackson Lecture given to the Neurological Section of the Royal Society of Medicine on November 22, 1949.

death-rate of 30–50 per cent. In the two subsequent years for which records are available (1946 and 1947) 76 and 68 cases have been notified. The cases following vaccination varied from 3 to 12 per annum in England and Wales during the years 1940–45. Evidence gleaned during the war from areas of Scotland where small groups of cases occurred showed that the incidence of encephalitis in relation to the number of vaccinations varied greatly. Fyfe and Fleming (1943) reported 8 cases among a group of 52,772 recently vaccinated persons in one district, and 1 case among 20,197 vaccinated in another district. In the Glasgow area Anderson and McKenzie (1942) reported 7 cases in about 500,000 vaccinations. No analysis seems to have been made of the incidence of encephalitis following measles or other infectious disease.

It is therefore clear that during the decade under review encephalitis has been rare in England and Wales. Personal experience indicates that the largest number of fatal cases falls in the group of post-infectious encephalitis following vaccination, measles, influenza or even mild coryza. No fatal case of this form of encephalitis following mumps has been recorded in this country although such cases have been reported from Canada (Donohue, 1941).

Other recorded or personally observed fatal cases fall into four fairly well-defined groups :

(1) Acute polioclastic or more pan-encephalitic type.
(2) Acute hæmorrhagic leuco-encephalitis.
(3) Subacute inclusion body encephalitis (Dawson, 1933).
(4) Subacute sclerosing (leuco-) encephalitis (van Bogaert, 1945).

In addition 3 non-fatal cases of louping ill have been reported, 2 in shepherds whose flocks were infected with louping ill. The other case occurred in a scientist doing field research on the disease (Davison, Neubauer and Hurst, 1948 ; Brewis, Neubauer and Hurst, 1949). The disease in these patients had a biphasic course rather resembling that of poliomyelitis, but the interval between the initial slight pyrexia and the later more severe attack of meningeal symptoms may be as long as a week. In 2 of these cases recovery was complete ; in the third slight hemiplegia was left. There have also been numerous cases with the symptomatology of benign lymphocytic meningitis, or mild encephalitis or encephalomyelitis affecting the brain-stem and spinal cord. Apart from those due to poliomyelitis some have been due to the Armstrong Lillie virus (lymphocytic chorio-meningitis,) but probably the majority are due to some other virus, e.g. psittacosis, influenza (Leigh, 1946) or mumps (Hammon, 1949). Some have been associated with a typical pneumonia (Holmes, 1947). So far as is known no fatal cases of this kind have occurred in this country.

(1) Acute Cases of Polioclastic Type

Ten fatal cases which fall into this class have been examined. A short report on the 8 cases seen during the war years has already been made for

the " Medical History of the War." In none of these cases was it possible to transmit the disease to laboratory animals.

In these 10 cases the duration of the disease has varied from two to three days to four weeks. In the more acute cases the onset was with headache, malaise and often vomiting, with fever, going on to delirium, drowsiness or unconsciousness, usually within three or four days. The degree of coma varied from case to case. In the case-notes such phrases are used as " drowsy but alert when roused," " looks about and mutters but appears not to understand when spoken to," " comatose, but can be roused momentarily by shouting his name," " unconscious, corneal reflex absent to cotton-wool but present to touch with finger." These descriptions may be compared with the deep sleep of the lethargica epidemic from which the patients " if aroused, wake up quickly and completely are orientated and fully conscious . . . but left to themselves soon drop back to sleep " (Economo, 1931) ; and also with Sydenham's description of *febris comatosa* " wherein the sick become stupid and delirious and sometimes he slept for some weeks and could be roused only by a great noise ; whereby being difficultly waked he would at length open his eyes, and having taken either a medicine or drink he fell asleep again."

The most abrupt onset was in the case of a woman of 35, who after a normal day's work was found in bed unconscious and remained so for seven days until death. This was the only case in which perivascular areas of softening in the basal ganglia were seen. The most slowly ingravescent case in this group was that of a woman with a vague history before admission to hospital of three to four weeks of severe headaches and attacks of weeping and shouting. In hospital she developed fever and and meningeal signs with increase of cerebrospinal fluid pressure to over 350 mm. of water.

Epileptiform fits occurred as an early symptom in 4 of the other cases, and in all of these they recurred during the course of the disease.

In 2 patients (Case 3, a boy of 9 years, and Case 7, a lad of 16 years) there was intense trismus, so that feeding by the mouth became difficult or impossible. In both cases this remained present till death. Oculomotor symptoms were not prominent in any of these cases. In Case 3 a left-sided external strabismus was noted and in Case 7 a slight left internal strabismus. The other cranial nerves also were rarely paralysed. In Case 1 there was weakness of the right side of the face associated with crossed hemiplegia of the left arm and leg ; difficulty in swallowing was a late symptom in Case 2. Nor was there much evidence of paralysis of the limbs, although weakness, sometimes hemiplegic in distribution, might be an early symptom. In the later stages the limbs might be flaccid or spastic, but the state of the deep reflexes was not always noted. The plantars also might give flexor or extensor responses. Neck rigidity and opisthotonus were equally variable.

The cerebrospinal fluid was examined in all the cases. In 3 it was quite normal (Cells 1, 2, 3 per c.mm. Total protein 15, 25, 45 mg. per 100 ml.).

In the others the cell count was raised in greater or less degree (13 to 550 cells per c.mm.). The cells were chiefly lymphocytes in all except one case in which an early puncture gave 10 polymorphonuclears and 3 lymphocytes per c.mm. The protein was relatively low in the early stages of the disease but rose later. Conversely the pressure which might be high (350 mm.–300 mm.) in the early stages tended to fall in the later stages. The glucose was always normal (58 to 75 mg. per 100 ml.). The chlorides were usually normal, but in Case 9 they were very low in the fluid obtained by the first 3 lumbar punctures (610, 590, 620 mg. NaCl per 100 ml.) and only rose to the neighbourhood of normal (700 mg.) a few days before death. There was no history of vomiting or diarrhœa in this case, and the reason for this fall was not clear.

Histopathology.—In most of these cases only selected portions were received for examination. These usually included some area of cortex and basal ganglia and the mid-brain and pons, but only the ventral or the dorsal or one lateral half of the brain-stem might be sent. The histological descriptions in almost all of these cases must therefore be considered incomplete and in some the amount and character of the tissue received was only enough to make the diagnosis of encephalitis reasonably certain. The degree of inflammatory exudate, and other evidence of encephalitis was extremely variable. In some cases perivascular infiltration in the brain-stem, basal ganglia, cortex or the white matter immediately under the cortex was the only evidence of encephalitis. In the cases with rather more severe lesions, the perivascular infiltrations were more widespread, and there was microglial hyperplasia in areas of the cortex, basal ganglia and brain-stem, with focal accumulations of such cells forming loose glial stars. Plasma cells appeared in the perivascular cuffs and free in the tissues. The nerve cells were little affected, but a few had a diffusely stained nucleus rather irregular eosinophilic cytoplasm with loss of Nissl granules (Hurst's eosinophilic degeneration). The presence of isolated cells of this character among a majority which retained a normal appearance was one of the most characteristic changes in cases of moderate intensity. It was chiefly seen in the cortex, but in Case 8 also in a few neurons in the substantia nigra (fig. 1). The characteristic eosinophilia was best seen in well-differentiated hæmatoxylin-eosin staining. The corresponding appearance in Nissl-stained sections (irregularity of the cell margins and loss of Nissl granules with a diffusely stained nucleus), was not so easily picked out. Neuronophagy was not seen in any case although a varying degree of satellitosis might be present in the cortex and basal ganglia.

In Cases 2, 3 and 9 the inflammation was of an intense character in the cortex and was widespread though less intense in the brain-stem and basal ganglia. In none of these cases, however, was the cerebellum affected.

In Cases 2 and 9, over fairly wide areas of cortex several centimetres in superficial extent, the nerve cells had been completely destroyed, being replaced by rounded cells with small round or irregularly shaped nuclei and clear or *slightly granular cytoplasm*. Most of these cells appeared to

be derived from microglia. Plasma cells were abundant especially immediately round the vessels but also free in the tissues. The astrocytes appeared to be preserved. This destructive inflammation was concentrated in the cortex, and though the neighbouring white matter also showed some inflammatory changes, these rapidly became less intense on passing away from the damaged areas of cortex. Characteristically also, in these two cases, neighbouring areas of cortex, e.g. the cortex on the opposite wall of a sulcus, were only mildly inflamed, showing cuffing of vessels and microglial infiltration but little damage to the neurons (fig. 2).

In Case 3 the lesions in the cortex, though very widespread and severe had produced less destruction of neurons. In this case the temperature had risen to 105° F. a few hours before death and as the post-mortem examination was not made till the following day, the cortical neurons all showed autolytic changes, such as darkly stained nuclei and loss of Nissl granules. Some, however, had undergone more severe damage. The degree of microglial proliferation was very striking in this case (*v.* Appendix).

Although the areas of perivascular necrosis in the basal ganglia seen in Case 1 and the cortical areas of complete neuronal destruction seen in Cases 3 and 9 are more in accord with histological descriptions of the North American forms of equine-encephalo myelitis than with those of encephalitis lethargica, there is no evidence in any of these cases of either the acute arteritis, or the massive collections of small round cells in the white matter which have been described in insect-borne types of encephalitis. The cases included in this group are definitely polioclastic, i.e. the inflammation is concentrated on and almost confined to grey matter. Within this limitation its incidence varies greatly ; in some cases it is most intense in the cortex, in others in the basal ganglia or brain-stem, where both the tegmentum and more ventrally placed nuclei such as the substantia nigra, nuclei pontis and inferior olives often show microglial excess with or without perivascular infiltration. In the one case in in which the cord is involved the inflammatory changes are most intense in the dorsal horns.

The meningeal exudate, which is often present, is usually concentrated round the larger veins. It is predominantly lymphocytic in character with a varying proportion of plasma cells and larger histiocytic cells. It is unprofitable to reopen here the old controversy as to whether this exudate is primarily meningeal or primarily intracerebral in origin (Hurst). All that can be said is that it is most in evidence over the areas of cortex which show the greatest inflammatory changes.

Although it would have been easy for American mosquitoes carrying encephalitis virus to have been brought to England during the war, the constant resistance of our cases to transmission to laboratory animals, in addition to their strongly polioclastic character, makes it unlikely that they belonged to any insect-borne type. The cases with slighter lesions resembled encephalitis lethargica in their histological appearances, and

were not clinically dissimilar. That this disease is still with us is suggested by the cases with pronounced oculomotor palsies recently reported by Leigh (1947) and by the occasional appearance of new cases of parkinsonism in young subjects. Histological studies combined with attempts to isolate virus will be needed in a considerably larger group of cases before this question can be settled.

(2) Acute Hæmorrhagic Leuco-encephalitis

In 1941 Weston Hurst gave the name "acute hæmorrhagic leuco-encephalitis" to an affection of the brain with rather characteristic features. It affected the central parts of the centrum ovale, sometimes more on one side than the other, sparing the poles of the hemispheres and spreading down to the crus of the mid-brain, the pons and the cerebellar peduncles. Macroscopically there were swelling and œdema and multiple small hæmorrhages. Microscopically he found intense polymorphonuclear exudate especially round the vessels, perivascular zones partial or more complete necrosis, and fibrinous exudate into and through the vessel walls. The cortex was only involved over the most intense lesions in the white matter.

Clinically both his cases presented themselves as hemiplegia of fairly rapid onset.

Similar cases have been reported by Henson and Russell (1942) and Greenfield (1942–3) in this country and by Adams, Cammermeyer and Denny-Brown (1949) from America and Norway. In one of Weston Hurst's cases, both the London cases and all 3 of the Boston cases, the disease came on after an infection of the respiratory tract, sore throat, influenza, coryza, or acute bronchitis.

The cerebrospinal fluid has shown a high cell count in many, although not all, of the recorded cases. In one of the Boston cases over 3,000 polymorphonuclear cells per c.mm. were counted, and in the case reported by the writer (1942–3, *v.* Appendix) there were 340 cells of which 84 per cent were polymorphonuclear. In a case at present under examination at the National Hospital (sent by Dr. Kirshner of Chichester) there were more than 1,200 cells of which 85 per cent were polymorphonuclear. In this case the disease came on two days after an attack of urticaria. Such a history suggests an allergic reaction of brain tissue, but eosinophil leucocytes were not prominent either in this case or in others reported.

The disease resembles closely some of the cases described at the end of the nineteenth century under the name "acute hæmorrhagic encephalitis." This name was used both for the cases in which the grey matter was chiefly involved and for the rarer cases, such as those described by Strümpell, in which the lesions were concentrated on the white matter of the hemispheres. The onset of the disease after a febrile affection of the respiratory tract often resembling influenza (Adams, Cammermeyer and Denny-Brown, 1949) and sometimes with an interval of a few days of

relative health, relates the disease to "post-influenzal" cases of acute disseminated encephalomyelitis (Greenfield, 1930).

Recent experimental work also has demonstrated a close relationship between these two diseases. It will be recalled that Rivers and his associates (1933, 1935) reported success in producing perivascular demyelinating lesions in monkeys by very numerous injections of extracts and emulsions of rabbit's brain. Kabat, Wolf and Bezer (1947) repeated these experiments, availing themselves of the "adjuvant" action of dead tubercle bacilli in oily emulsion to increase the production of antibodies. After only three injections 17 out of 19 monkeys showed neurological symptoms, and in those which died or were killed soon after the onset of symptoms the lesions were remarkably similar to those of acute hæmorrhagic leuco-encephalitis," e.g. œdema, perivascular hæmorrhages, fibrin in the vessel walls, and an exudate of neutrophil and occasional eosinophil leucocytes as well as perivascular demyelination. Morgan (1947) independently obtained similar results but gave a less complete histological description. In later experiments of the same kind, but using guinea-pigs, these more acute changes were not seen, but perivascular zones of demyelination with microglial proliferation were produced closely resembling the appearances in the post-infectious form of encephalitis (Lumsden, 1949). It is interesting also to note that in other recent work of this kind by Freund, Stern and Pisani (1947) and by Lumsden (1949) there were also reactions of more granulomatous character in the walls of some vessels and under the walls of the ventricles with no zone of demyelination around them.

Thus it appears possible to obtain by subcutaneous injections of a mixture of the same substances, but in different quantities and in different animals, lesions of three different kinds.

(1) Granulomatous lesions consisting of proliferated endothelial cells in the vessel walls.

(2) Perivascular demyelination with microglial proliferation.

(3) Fibrinous and polymorphonuclear exudate into and through the vessel walls with œdema and hæmorrhages.

The two latter may be different grades of the same reaction, but it is noteworthy that in his original description Weston Hurst did not find fibrinous exudate and perivascular demyelination in relation to the same vessel. In other cases, however, these lesions are combined (fig. 3). Nor is it usual to find the more acute exudatixe reactions in cases of post-infectious encephalitis. That both these forms of reaction may be allergic seems to be proved by the experiments cited, since adjuvants which increase antibody formation greatly facilitate the production of the characteristic lesions in the brain, and skin tests prove that the animals are allergic to the material injected. The relation of perivascular demyelination to granulomas in the walls of the vessels is still less clear. The latter have no exact counterpart in human encephalitis, but are the kind of simple local allergic reaction which one might expect to the presence

of antigen in the circulating blood. Their occurrence without demyelination in certain experiments (Freund, Stern and Pisani) and in relatively insusceptible animals such as the guinea-pig suggests that they may be an early stage of reaction which may be replaced or superseded by perivascular demyelination or necrosis. This latter reaction has been explained on the assumption that anti-brain antibodies are formed at the site of injection and act on the brain by passing through the walls of some of the venules.

The relation of these experimental results to the naturally occurring diseases in man needs further clarification. But they at least indicate that diseases which have been separated on histological grounds may actually be produced by the same or a similar mechanism acting with a different intensity, or in patients with a different allergic constitution. For example, vaccinia virus usually produces in the brains of animals meningeal inflammation and small granulomas in relation to vessels. (McIntosh and Scarff, 1930; Hurst and Fairbrother, 1930). Similarly in mumps the lesions are presumed to be usually meningeal; but in both diseases one may, under certain conditions as yet unknown, get an encephalitis of the post-infectious type, i.e. perivascular demyelination, or partial softening, with intense microglial reaction in this zone but without any diffuse meningeal reaction. Similarly after respiratory infections one may get the common picture of acute post-infectious encephalitis or much more rarely that of acute hæmorrhagic leuco-encephalitis. Future research might well be directed to assessing the degree of immunity or allergy to the virus of influenza or other possible cause of the respiratory disease in cases of these kinds.

(3) Subacute Inclusion Body Encephalitis

The condition termed "subacute inclusion encephalitis" by Dawson (1933–34), presents a very different and rather distinctive clinical course. The 10 cases so far reported or personally examined have all been in children between the ages of 4 and 16 and in all except one below 11 years of age. The disease is ingravescent, gradually producing symptoms over a period of weeks. There is a ruthlessly progressive course, to a condition of complete loss of mentality, usually associated with rigidity resembling that of a decerebrate animal. But at an earlier period of the disease, in all but 2 cases, myoclonic jerking movements or rapid spasms of the face or limbs or the entire body have been observed. The cerebrospinal fluid, though otherwise normal, has given a Lange reaction in the paretic zone in all the cases in which it has been examined. Death has occurred at an interval of seven weeks to six months from the first symptoms.

A series of 4 cases of this kind has recently been recorded (Brain, Greenfield and Russell, 1948) and 3 further cases, 2 of which were typical, have been examined at the National Hospital (*v* Appendix).

The histological appearances seen in such cases are quite characteris-

tic. Perivascular infiltration and microglial hyperplasia are widespread in the cortex and are combined with a varying degree of astrocytic gliosis, so that the cortex may be firmer to the touch than normal. Similar subacute inflammatory lesions may be seen in the basal ganglia, especially the thalamus, and in the grey nuclei of the brain-stem. In one case the ventral and dorsal horns of the cervical cord were involved. In the affected areas a varying proportion of the neurons are degenerated, showing at first a condition resembling central chromatolysis, but later complete loss of Nissl granules, and shrinkage of the cytoplasm. Neuronophagia is commonly seen. Eventually the most affected neurons disappear completely. In many of the degenerated neurons acidophilic hyaline inclusion bodies are seen both in the nucleus and cytoplasm. In both situations they are at first small and multiple, both soon fuse into larger masses and eventually hyaline inclusion material fills the nucleus being covered only by the nuclear membrane and a few granules of nuclein. At this stage the cell body may have shrunken so as to be almost unrecognizable or may consist of a rounded mass of inclusion material (fig. 4).

This form of encephalitis is definitely polioclastic with no more alteration in the white matter than can be accounted for by destruction of cortical neurons, or spread of inflammation into the sub-cortical zones. In this respect, as also in the appearance of the inclusions, it differs from the acuter cases of encephalitis with intraneuronal inclusions due to the virus of herpes febrilis. In 6 of these 10 cases unsuccessful attempts have been made to transmit the disease to animals.

NOTE.—Three further cases which appear to belong to the same group have recently been reported from the U.S.A. by Malamud, Haymaker and Pinkerton (1950). The ages of these patients were 17, 9 and 17 years at death, and the duration of the disease respectively nine months, twenty-one months and seven years. Myoclonic jerkings were present in the first case, which also gave a paretic Lange response in the cerebrospinal fluid. In the second case there were " clonic spasms occurring every six seconds." In their third case "there were momentary spells of unconsciousness initiated by turning movements to the right," and occasional " Jacksonian-like attacks confined to the right lower extremity." The histological appearances in these cases differed from those previously reported in (1) the absence of intra-cytoplasmic inclusions ; (2) the greater degree of degeneration of the white matter of the brain ; and (3) in the case with seven years' history, the presence of neurofibrillary changes of Alzheimer type in the neuron of the cortex, thalamus, substantia nigra and brain-stem. In none of these cases were attempts made to transmit the disease to animals.

(4) The clinical picture of this condition differs very little from that of the form of subacute encephalitis described recently by van Bogaert under the name of " subacute sclerosing leuco-encephalitis." In the cases he described, also in children between $5\frac{1}{2}$ and 14 years, the symptoms began insidiously ; for example in one of his cases the first evidence that anything was wrong was that the child, previously a bright scholar, had done very badly at school in the autumn term. In this disease also involuntary movements are characteristic of the middle period. They may

resemble those of inclusion body encephalitis, e.g. sudden jerkings, defensive movements, hemiballismus or rather characteristic torsion movements beginning with the head, followed by a turning movement of the body in the same direction, usually accompanied by some degree of opisthotonus. In a case material of which was sent to me from Leeds by Dr. Garland, there was parkinsonian immobility. Another feature common to these two forms of subacute encephalitis is the colloidal reaction in the cerebrospinal fluid which, though not so constantly abnormal in this as in the former type, may show curves in the *paretic* or *luetic zones* with little other abnormality. The duration of the disease is also similar. In van Bogaert's and Bodechtel and Guttmann's cases it was from three to five months; in our case, six months; Rosanoff's (1947) first case, which appeared to be similar, had the rather longer duration of nine months.

Histologically these cases show a widespread but focal inflammation of the brain not limited to the grey matter but affecting the white matter to at least an equal degree. The centrum semiovale shows rather ill-defined areas of partial demyelination in which the myelin stains less deeply than elsewhere. Fat granule cells may be diffusely scattered through these areas or may only be seen round the vessels. There is a diffuse mobilization of microglia, infiltration with plasma cells and above all a diffuse neuroglial sclerosis. Van Bogaert considered the gliosis to be out of proportion to the myelin loss. A similar sclerosis is also present in the cerebral cortex with microglial proliferation but with comparatively little evidence of neuronal damage, e.g. in our case there were many pairs or quadruplets of astrocyte nuclei in the cortex and slight swelling of the cell bodies of the astrocytes with early formation of neuroglial fibres. The name *subacute sclerosing encephalitis* therefore appears fully justified. Dr. van Bogaert's term "leuco-encephalitis" emphasizes the characteristic damage to the white matter, but leaves out of account the cortical changes which are also important. Perhaps the term "Pan-encephalitis" already adopted by Pette (1942) for forms which attack both grey and white matter could be usefully employed here, i.e. "Subacute sclerosing pan-encephalitis."

It is not always easy to distinguish these two forms even on histological grounds, as in the inclusion form also some degree of demyelination of the white matter is seen in relation to the more severely affected areas of cortex. In some cases of this type the greater part of the cerebral cortex may show no more severe changes than those seen in van Bogaert's type, but in a few areas more evidence of neuronal destruction or degeneration will be found and a careful search of these areas with the oil immersion objective will reveal the typical inclusion bodies. The author's experience indeed is that the more thoroughly the cerebral cortex is searched in subacute cases the more of them will be found to be of inclusion body type. This statement is not intended to suggest that van Bogaert's type has no existence in fact; on the evidence available this

histological picture may be characteristic of certain subacute cases and may be caused by more than one virus, but experience in this country and in the United States indicates that it is less common than the inclusion body type.

This disease has an interesting parallel in the subacute progressive form of encephalitis in the moose in the North-Eastern states of America, well described by Lester King (1939). Here also there are scattered, ill-defined areas of partial demyelination with a disproportionate overgrowth of neuroglial fibres, and an accompanying inflammatory reaction which may be primary or secondary. Two differences are (1) the limitation of the disease to the white matter, and (2) the absence of anisotropic lipoids in the process of myelin katabolism, recalling the condition in some forms of diffuse sclerosis of the brain in children. This disease of the moose has so far resisted attempts at transfer to laboratory animals.

In spite of failure to transmit these two human forms of subacute encephalitis to animals there are strong arguments in favour of placing them in the group of inflammatory diseases probably due to a virus. In the inclusion body form these bodies resemble, to some degree, those seen in herpes febrilis and other virus diseases, and the evidence of polioclastic encephalitis is otherwise definite enough. In the sclerosing type also there is characteristic inflammation of the brain tissue though of a more diffuse character. The partial demyelination and sclerosis appear to be secondary to this.

All who have examined many cases of encephalitis have probably seen also cases of subacute progressive encephalitis which do not fit into either of these two categories. In them the disease may be of polioclastic type without inclusion bodies or a pan-encephalitis with the formation of cysts by necrosis of the white matter as in the equine and Japanese forms (Rosanoff, 1947). The nosological grouping of these cases is a matter for the future. Some may be related to known forms of acute encephalitis, others to forms not yet described or they may be separate disease entities.

The conception that encephalitis may occur in a subacute progressive form, although suggested by some cases of post-lethargic syndromes, has only recently been fully documented. Few have worked in this field, but it is one which is full of interest and offers a rich harvest.

In conclusion I desire to express my gratitude to all those who have sent me material from cases of encephalitis, and who have allowed me access to case histories. Special thanks are due to Sir William Jameson for allowing me to report on material obtained through the Ministry of Health.

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PLATE IV (*see overleaf*)

FIG. 1. (*Case* 8).—Eosinophilic degeneration of neurons. (*a*) Substantia nigra, showing one neuron with slight eosinophilic degeneration and other healthy neurons. (*b*) and (*c*) Cerebral cortex; one healthy and two degenerated nerve cells are seen in each figure. Alum hæmatoxylin-eosin. × 460.

FIG. 2. (*Case* 9).—(*a*) Insular and (*b*) opercular cortex. The insular cortex is very heavily infiltrated, and appears as an almost solid mass of cells with heavy infiltration of emerging veins. (*b*) At the opposite side of the fissure the opercular cortex shows only moderate perivascular infiltration. Iron-hæmatoxylin. van Gieson. × 25.

PLATE V

FIG. 3 (*Case* 10).—*Acute hæmorrhagic leuco-encephalitis.* (*a*) Corpus callosum, gyrus cinguli and neighbouring gyri showing perivascular zones of demyelination and small hæmorrhages (black). Loyez' myelin stain. × 3. (*b*) Subcortical white matter to show fibrinous exudate in and through the vessel walls and pallor of myelin staining in a narrow zone surrounding this. Note that there is no thrombosis in this vessel. Mallory's phosphotungstic acid hæmatoxylin. × 200.

PLATE VI

FIG. 4 (*Case* 13).—*Subacute inclusion body encephalitis.* Four cortical nerve cells. Two, (*a*) and (*b*), are relatively healthy but contain an intranuclear inclusion body surrounded by a clear halo. In two, (*c*) and (*d*), the nucleus is almost filled by inclusion body and the cytoplasm is degenerated, and in (*d*) is filled with hyaline eosinophilic material. Alum hæmatoxylin-eosin. × 1,300.

FIG. 5 (*Case* 14).—*Subacute sclerosing encephalitis.* Sections from the white matter of the occipital lobe (*a*) external to the ventricle at the point marked x in (*b*). (*a*) Stained by Sudan IV and alum-hæmatoxylin to show fat granule cells with many intact myelin fibres. × 200. (*b*) Stained by Anderson's method for neuroglial fibres. × 8.

APPENDIX

REPORTS OF INDIVIDUAL CASES

I. ACUTE POLIOCLASTIC GROUP

Case 1.—F. W., female, aged 35. Duration of disease seven days. (Material received from Dr. J. S. Faulds, Carlisle General Hospital.)

History.—On the night of November 10–11, 1941, the patient went to bed between midnight and 1 a.m. as usual. She had been well up till this time. At 6 a.m. on the 11th she was found unconscious in bed, and was transferred to the Carlisle General Hospital.

On examination here the pupils reacted to light; there was general flaccid paralysis, with flexor plantar responses. The following day she developed left-sided hemiplegia with weakness of the right side of the face and conjugate deviation of the eyes to the right. The abdominal reflexes were absent. Kernig's sign was negative. Lumbar puncture was done twice. The C.S. fluid contained 1 cell, 15 mg. protein, 775 mg. NaCl per 100 ml., W.R. negative. No barbiturates were found in the C.S. fluid. Blood glucose 139 *mg. per cent.* Blood urea 41 mg. per cent. She died on November 18 without regaining consciousness.

A post-mortem examination was made on November 19 by Dr. Faulds. The organs of the body cavity showed terminal congestion of the lungs and cloudy swelling of the liver. The brain appeared congested and swollen. Pieces from two areas of cortex, the basal ganglia, including the thalamus, globus pallidus and putamen, the pons (two levels) and the medulla were received from Dr. Faulds.

In the *cortex* the only lesion seen was lymphocytic infiltration in the wall of a small subcortical vessel. In the posterior pole of the *globus pallidus* two areas of necrotic softening were seen. Round both there was a zone in which the endothelium of the capillaries was swollen. In the centre, which was otherwise necrotic the vascular endothelium and microglial cells were preserved. Fat granule cells, some in mitosis, were seen in the outer zone. Some threads of fibrin, indicating terminal clotting, were seen in a small vein beside the lesions, but there were no other evidences of vascular occlusion. A small vessel in the centre of the postero-external lesion showed no fibrin. The two areas were of the same age, which might well have been eight days. There was no inflammatory infiltration in the neighbourhood of these lesions. Lymphocytic cuffing was seen also in small vessels in the medulla at the level of the pyramidal discussation and in the ventro-lateral area of the pons, where a small glial star was also present.

Comment.—The lesions in the globus pallidus are similar to those of C.O. poisoning, but they were very small, and no alteration in the cortical nerve cells were seen, such as would account for the prolonged coma. On the other hand the perivascular infiltration and glial stars made the diagnosis of encephalitis reasonably certain.

Case 2.—Pte. T. E., male, aged 20. Duration of disease eight days. (Material received from Major R. W. Fairbrother at the request of Lt.-Col. Bensted.)

History.—On January 3, 1942, the patient had the symptoms of a cold and headache which became more severe. He reported sick on January 5 with a temperature of 100° and was admitted to hospital where he was said to have had two fits. On January 6 he was transferred to Davyhulme Military Hospital where he appeared drowsy but alert when roused. On January 7 the C.S. fluid obtained by lumbar puncture contained 66 cells per c.mm., chiefly lymphocytes. On January 8 he was incontinent and in the afternoon had difficulty in swallowing and in breathing. He became semicomatose, and had severe epileptiform seizures involving mainly the right side. During the next three days his condition deteriorated rather rapidly. He was at first co-operative during examination, but unable to speak. Later he lapsed into coma and died at 6 a.m. on January 11. Dr. Fairbrother made the post-mortem examination, injected suspensions of brain into mice, without ill effect, and sent glycerinated material to Professor McIntosh who obtained no better result.

The material received in formol-saline included cerebral cortex and underlying white matter, the cornu ammonis and inferior temporal cortex, thalamus, putamen and nucleus subthalamicus and medulla and spinal cord.

The meninges showed patchy lymphocytic infiltration, largely perivascular, with an excess of microglial cells in the first layer of the underlying cortex in areas where meningeal infiltration was most intense. The cortex was in some areas very severely degenerated, while in other areas it showed fairly intense inflammatory infiltration but less neuronal damage. In some severely affected areas of cortex, one of which

PLATE IV

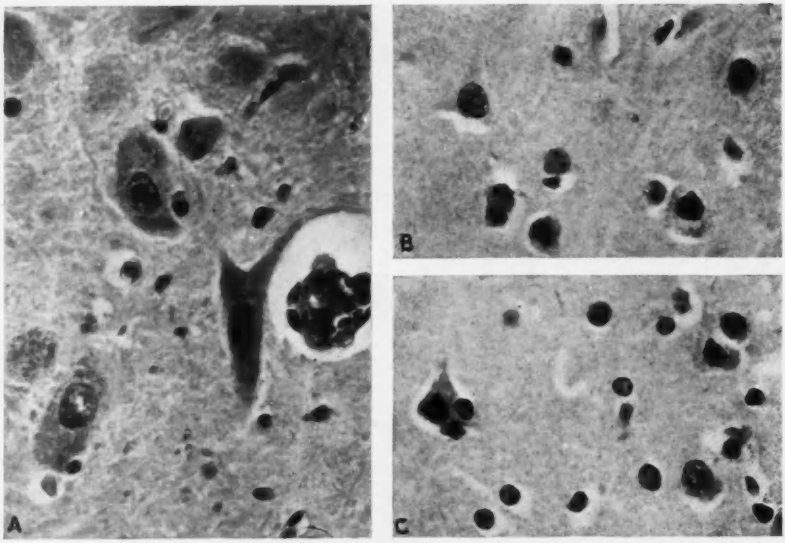

FIG. 1

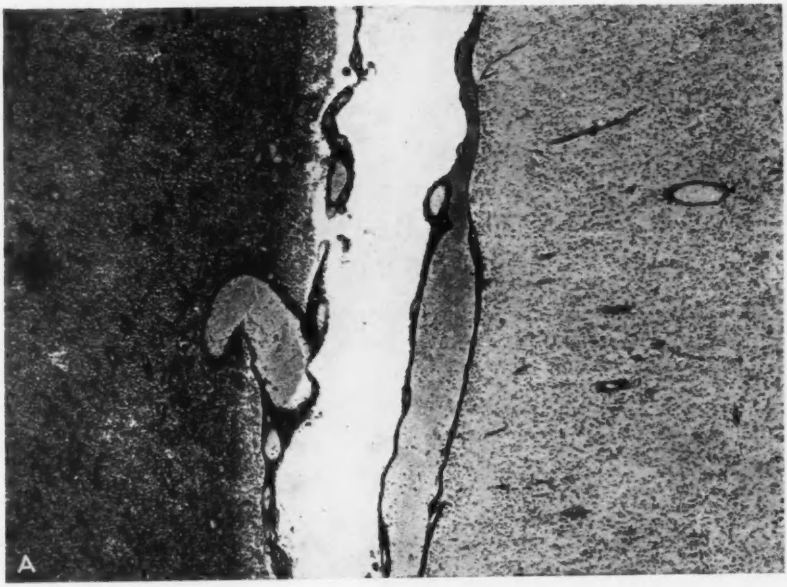

FIG. 2

To illustrate article by J G. Greenfield.

PLATE V

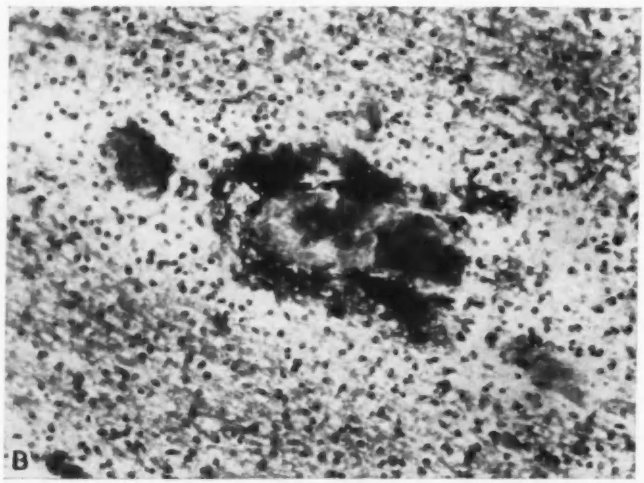

FIG. 3

To illustrate article by J. G. Greenfield.

PLATE VI

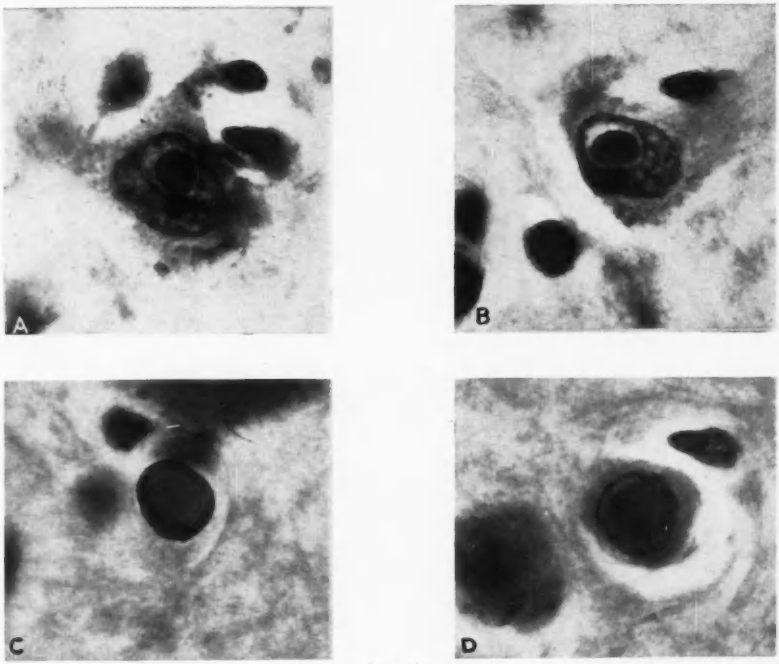

FIG. 4

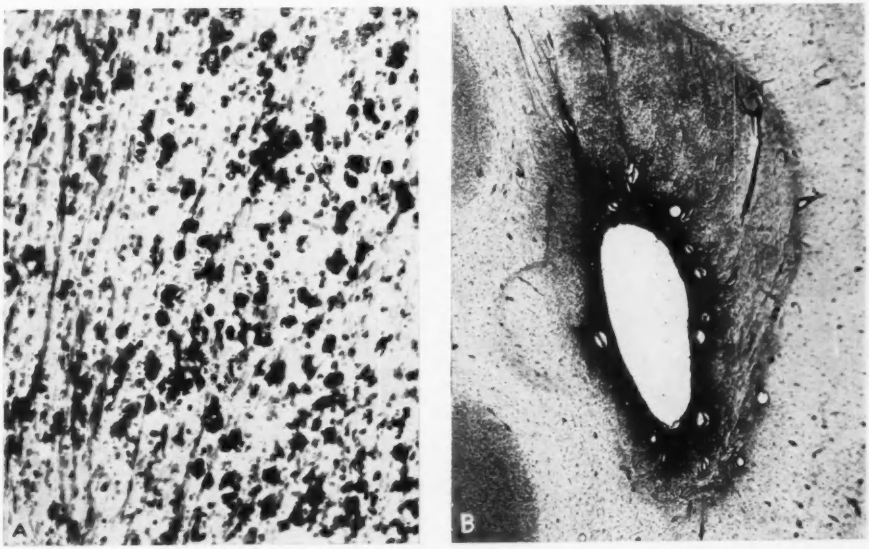

FIG. 5

To illustrate article by J. G. Greenfield.

measured 3·5 cm. in the section, there was intense congestion of the superficial and cortical vessels without thrombosis. All the neurons here were shrunken with pale elongated angular nuclei and eosinophilic cytoplasm. The astrocyte nuclei appeared intact, and their cell bodies were not enlarged. The microglia was greatly proliferated especially round some vessels. There seemed to be disappearance of many oligodendroglial nuclei, as few were seen, so that the cortex appeared less cellular than normal, in spite of the excess of microglia. A few glial stars were seen. A few neurons were undergoing neuronophagy, but most had no satellites or phagocytic cells round them. A few of the vessels were cuffed with lymphocytes; no plasma cells were seen. In less damaged areas there was more intense perivascular cuffing, but most of the neurons were well preserved. A few glial stars were seen, but there was less microglial hyperplasia. The pyramidal layer of the hippocampus showed as severe neuronal damage and excess of microglia as the most affected areas of cortex; neuronophagy was fairly common here. In the layer of the fascia dentata a few neurons persisted in a condition of eosinophilic degeneration but most had disappeared and had been replaced by microglial cells which infiltrated this layer rather heavily.

In the *thalamus* there was an area of almost complete necrosis without cellular reaction of any kind as well as less degenerated areas in which there was much microglial proliferation with minor degrees of neuronal degeneration. There was a varying degree of infiltration both of tissues and vessel walls in the thalamus and nucleus subthalamicus. In the white matter under the most severely affected areas of cortex many of the vessels had a narrow cuff of lymphocytes in the perivascular sheath and there was a narrow zone of microglial proliferation round this. Both forms of infiltration were, however, less intense than in areas of cortex which were comparatively lightly affected.

In the *medulla* a few glial stars were seen in the inferior olive and there was lymphocytic cuffing round some vessels under the floor of the fourth ventricle. Loose aggregations of microglial cells were also seen.

Sections of the spinal cord appeared normal.

Case 3.—N. B., male, aged 9. Duration of illness six to seven days. (Brain received from Hertford County Hospital, Dr. H. F. Barnard.)

History.—On August 22, 1942, he felt unwell and vomited several times. The next day he complained of headache, and the day following was drowsy and hallucinated in the morning and became unconscious in the evening. He was admitted to Hertford County Hospital on August 25, comatose, but shouting his name roused him for a second or two. His teeth were tightly clenched and separation of them was much resented. There was some neck rigidity on full forward flexion and Kernig's sign was present on both sides. The pupils reacted through a small range to light. There was a left-sided external strabismus. The optic discs were sharply outlined. A grasp reflex was present; the tendon reflexes were present; the abdominal reflexes were absent and the plantars flexor in type. Lumbar puncture gave a clear fluid under a pressure of 80 mm. It contained 1 lymphocyte per c.mm. and 25 mg. per cent protein. Coma continued during the ensuing days, but the child could be roused as before into semiconsciousness in which he was resentful. Trismus continued. On the 28th at 12.30 p.m. the temperature had risen to 105°. The arms, which before had been strongly flexed were now extended, sometimes stiffly. The pupils still reacted and the corneal reflex could be elicited by touching with a finger, but not by cotton-wool. The patient died at 3 p.m. on the same day.

A post-mortem examination was made by Dr. Barnard on August 29. No disease was found in the organs of the body cavity. Pieces of brain and spinal cord were received in formol saline.

Throughout all areas of the *cerebral cortex* examined there was a varying degree of perivascular infiltration, in which lymphocytes predominated, but plasma cells

and histiocytes were also seen. There was also an increase in number and size of microglial nuclei; this was everywhere present and in some areas very striking. The astrocyte nuclei were often in pairs, indicating recent division. The nerve cells all showed shrinkage of the cytoplasm and basophilia of the nucleus, which was interpreted as being due to the high temperature before death and to post-mortem autolysis. In some neurons the changes were rather more severe than in others, but characteristic eosinophilia was not seen.

The *putamen* was as severely affected as the cortex. A few vessels here showed recent thrombosis. In the globus pallidus there was perivascular infiltration and diffuse slight microglial proliferation, but much less than in the putamen. The caudate nucleus, where examined, was practically normal.

The *thalamus* was diffusely, but not uniformly, affected with microglial hyperplasia, but the nerve cells appeared fairly normal.

The *nucleus subthalamicus* showed no abnormality. The *substantia nigra* and *nucleus ruber* on one side were normal except for the presence of a glial star in the latter, but on the other side the middle area of the substantia nigra and nucleus ruber showed considerable microglial hyperplasia and cuffing of vessels. Little abnormality was seen in the walls of the third ventricle.

In the *pons* there was diffuse microglial proliferation among the nuclei pontis and a cuffed vessel was seen under the floor of the fourth ventricle. The *cerebellum* and cerebellar peduncles showed no lesions. The medulla was not received. In the *spinal cord* at the mid-cervical level (C.5) there was perivascular infiltration and diffuse microglial proliferation at the base of the ventral horn and in the dorsal horn on one side, and of less intensity and more limited to the central area of grey matter on the other side. The neurons of the ventral horns appeared normal. At the mid-thoracic level one dorsal horn showed fairly severe infiltrative lesions, while the rest of the grey matter was normal. No lesions were seen in the lumbar cord.

A careful examination was made for inclusion bodies but none were found. The cornu Ammonis was much less affected than the rest of the cortex and in its anterior end was quite normal, a finding which was against the possible diagnosis of rabies.

Case 5.—D. C., female, married (age not stated). Duration of illness four to five weeks. (Material received from Lister Hospital, Hitchin.)

History.—There had been a rather vague illness for three or four weeks before admission to hospital, in which the patient had complained of severe headaches and had given way to outbursts of weeping or shouting. On admission to hospital on November 15, 1942, there were meningeal signs and lumbar puncture gave C.S. fluid under more than 350 mm. of pressure. It contained 104 lymphocytes per c.mm., protein 60 mg., NaCl 740 mg. Glucose 58 mg. per 100 ml. On November 16 the C.S. fluid contained 88 lymphocytes per c.mm. Protein 60 mg., NaCl 690 mg. Glucose 75 mg. She died with a gradually rising temperature on November 18.

Histological examination showed perivascular lymphocytic infiltration and diffuse microglial hyperplasia and proliferation in all areas of the cerebral cortex examined. The perivascular cuffs were up to three cells thick and were abundant in some areas of the cortex. The hippocampus in this case was rather less affected than other areas of the cortex. The cortical neurons and astrocytes did not appear to be altered. In the meninges there was some perivascular infiltration in which also lymphocytes predominated. The white matter except immediately under the cortex and the basal ganglia (thalamus, putamen and globus pallidus) were quite normal except for an occasional cuffed vessel under the wall of the third ventricle. The nucleus subthalamicus and substantia nigra showed no lesions.

The *cerebellum* was also normal. In the nuclei pontis there appeared to be a slight excess of microglial cells and in the inferior olives they formed small collections rather less closely set than in glial stars. The thoracic cord was normal.

Case 8.—P. S., female, aged 15. Duration of illness five days. (Material received from the Park Hospital, Hither Green, by the courtesy of Dr. Stanley Banks and Dr. Cruickshank.)

History.—She felt unwell on July 26, 1946, and on July 28 and 29 had epileptiform fits. On July 30 she was admitted to hospital in coma with stertorous breathing and hyperpyrexia. There was slight neck stiffness. The left plantar reflex was extensor in type. The cerebrospinal fluid obtained by lumbar puncture contained 220 cells per c.mm. of which 80 per cent were lymphocytes, protein 90 mg. per cent, NaCl 74 mg. per cent. No micro-organisms were found in it. The lower face was weak on the right side ; she was able to swallow. In the middle of the night of July 30–31 she stopped breathing for two or three seconds, the face was white and the pulse very rapid. After an injection of lobelin breathing became rapid and shallow, 40–50 per min. She died at 8.40 a.m. the next day. Dr. Marshall Findlay attended the post-mortem examination and excised a piece of mid-brain aseptically : he injected an emulsion of this into rabbits, guinea pigs, mice and a monkey intracerebrally, but without result.

Post-mortem findings.—The lungs were in a condition of hæmorrhagic bronchopneumonia. The heart, liver and kidneys showed cloudy swelling.

Histology of brain and spinal cord.—In the *cerebral cortex* a large number of the pyramidal cells were in eosinophilic degeneration (fig. 1) which was often quite marked. Eosinophilic cells were in a minority, however, and lay among cells which appeared quite normal. There was no cuffing of vessels here nor any noticeable microglial hyperplasia. The superficial meninges showed mild lymphocytic infiltration.

In the *nucleus caudatus* there was slight perivascular infiltration by lymphocytes and histiocytes, and focal infiltrations of the tissues by plasma cells and microglial cells. No abnormality was seen in the *putamen.*

In the *mid-brain* there was perivascular infiltration by lymphocytes and histiocytes with an occasional polymorphonuclear leucocyte. In the substantia nigra a few cells were in eosinophilic degeneration (fig. 1) and there were many focal collections of microglia.

In the ventral part of the *pons* focal microglial proliferations were seen among the nuclei pontis. Many of the nerve cells had undergone eosinophilic degeneration.

The *spinal cord* showed no lesions.

The histology in this case was more reminiscent of that of encephalitis lethargica than in any of the other cases examined during the period under review. The limitation of the inflammatory lesions to the pons, mid-brain and basal ganglia, with apparently primary degenerative changes in the neurons of the cortex, substantia nigra and nuclei pontis closely resembled what was found during the lethargica epidemic. The amount of cortex examined was not sufficient to make it certain that no inflammatory changes were present there, but in the pieces examined the neuronal degeneration was the only obvious change except for some meningeal exudate.

Case 9.—J. B., female, aged 20. Duration of disease three weeks. (Material received from Dr. Sleigh Johnson, Chelmsford and Essex Hospital, through the courtesy of Dr. D. J. O'Brien.)

History.—She was admitted to Heybridge Isolation Hospital on January 15, 1947, as a case of cerebrospinal meningitis. The history then obtained was that she had had headache since January 12 and on the day of admission had a fit. On admission she was mentally alert, but had a rather abrupt manner. On the 17th she became mentally deranged and did not recognize her parents. The next day she talked incoherently and on the 19th she had one fit during the day and two at night. Cerebrospinal fluid obtained by lumbar puncture on January 18 contained 20 lymphocytes per c.mm., protein 25 mg., NaCl 610 mg. per 100 ml.

She was transferred to the Chelmsford and Essex Hospital on January 20. On admission she was unconscious but reacted to painful stimuli. There was slight neck rigidity. The pupils reacted briskly to light. All the limbs, especially those on the right side, were spastic. The tendon-jerks were exaggerated, the right plantar response of extensor type. A lumbar puncture on this date gave C.S. fluid at over 300 mm. of pressure. It contained 550 cells per c.mm., mainly lymphocytes, protein 110 mg., NaCl 620, glucose 66 mg. per 100 ml.

On January 22 she was more deeply unconscious, she looked about her and muttered, but did not understand when spoken to.

On the 24th the C.S. fluid pressure was 250 mm. It contained 216 lymphocytes per c.mm., and protein 110, NaCl 620, glucose 66 mg. per 100 ml.

On the 29th the C.S. fluid pressure was 125 mm. There were 210 lymphocytes per c.mm., protein 50 mg., NaCl 700 mg. per 100 ml. She remained deeply unconscious with increasing spasticity of the limbs but responded to painful stimuli till near the date of her death on February 2, 1947. Her temperature charts showed an irregular pyrexia between 100·4° and 104° from January 15 to 20. The temperature fell to normal on the 24th and remained between normal and 101·2° until death.

Post-mortem examination.—Brain: On naked-eye examination there was hæmorrhagic congestion resembling infarction in the right hippocampal gyrus external to the cornu Ammonis. There was also intense congestion on the mesial surface of the right frontal pole and the island of Reil was similarly affected. On the left side also there were several areas of hæmorrhagic congestion. An older hæmorrhagic area was seen in the posterior part of the left hippocampal gyrus.

Histology.—The right insular cortex and areas of similar macroscopic appearance consisted of an almost solid mass of rounded phagocytic cells with a rather granular unstained cytoplasm and one or more small rounded central or eccentric nuclei. Larger oval astrocytic nuclei were present and round some of them there was a swollen cell body about the same size as the nucleus; some nuclei were paired, others enlarged and hyperchronic. No neurons could be found. There were widespread and intense perivascular infiltrations in which plasma cells predominated and numerous plasma cells lay in the tissues near these vessels. Many large clear cell bodies contained anisotropic hæmatin crystals. The blood vessels were distended but not thrombosed. The overlying meninges were infiltrated with lymphocytes and plasma cells which formed dense accumulations round the vessels. In the white matter underlying severely inflamed areas of cortex there were many astrocytes with greatly swollen cell bodies: some of these had a pale degenerated nucleus (fig. 2).

In the opercular cortex contiguous with the very inflamed insular cortex, the lesions were comparatively slight. Many vessels were cuffed by a single zone of lymphocytes and there was microglial proliferation and an occasional plasma cell in the tissues. Here many of the nerve cells contained hæmatin crystals and some showed slight autolytic changes. In other areas of cortex an occasional cuffed vessel and slight microglial proliferation were the only evidences of disease.

The *basal ganglia* showed widespread lesions of medium severity such as cuffing of an occasional vessel, some microglial proliferation and pairing or swelling of astrocytic nuclei.

The *substantia nigra* showed minimal lesions, an occasional loose glial star and one cuffed vessel being the only obvious changes. Rather more intense focal and diffuse microglial proliferation was seen under the walls of the third ventricle, but no degeneration of neurons was seen here. Glial stars and an infiltrated vessel were also seen in the nucleus ruber, but dorsal to this in the upper tegmentum more intense lesions were present.

The spinal cord was normal except for fairly heavy lymphocytic infiltration of the meningeal vessels.

II.—Acute Hæmorrhagic Leuco-encephalitis

Case 10.—B. L. H., male, aged 51. Duration of illness three days. (Under the care of Dr. Allan Birch at Chase Farm Hospital.) This case was referred to briefly by the author in the discussion at the Royal Society of Medicine in 1942–43.

History.—According to his private doctor, Dr. Artrick of Enfield, he had been bronchitic for some years. He called Dr. Artrick in on August 23, 1941, for a febrile illness with symptoms of malaise and attacks of shivering, which he had had for about a fortnight. Dr. Artrick found evidence of acute, on the top of chronic, bronchitis. On August 25 Dr. Artrick was called in again and found the patient very quiet, only responding to his Christian name. He sent him to Chase Farm Hospital next day. The patient was then comatose, cyanotic and breathing heavily at 36 per minute. Rhonchi and coarse râles were heard all over the chest. The pulse was 100 per minute. B.P. 130/80. The liver was felt three fingerbreadths below the costal margin. The pupils reacted to light and the optic discs had sharp margins. All the limbs were spastic and the deep reflexes present. The plantar reflexes were extensor in type. There was moderate neck rigidity and Kernig's sign was positive.

A lumbar puncture was performed and 3 ml. of colourless opalescent fluid with a fine coagulum obtained. It contained 342 leucocytes per c.mm. (84 per cent polymorphonuclear), protein 60 mg., NaCl 760 mg., glucose 62 mg. Cultures were sterile and no organisms were seen in films of the deposit.

He remained unconscious but irritable, plucking at the bed-clothes. At 4.45 p.m. on August 26 a Jacksonian attack occurred affecting the right face, limbs and trunk. He was very cyanosed during the attack. After it all his limbs were hypotonic, the right more than the left.

On August 28 at 10.30 a.m. he had a second right-sided Jacksonian attack lasting half an hour. After this the temperature rose to 104° F. He remained comatose and cyanosed. The retinal veins were congested and the discs pink, but there was no papillœdema. The pupils remained active to light. The deep reflexes and plantar responses were absent. He died at 3.50 p.m. on the same day.

At the *post-mortem examination*, made twenty-two hours after death, the left lung was found slightly adherent to the chest wall with semipurulent lymph. The right lower lobe was congested with some hæmorrhages and small foci of bronchopneumonia. The left upper lobe was congested and œdematous. The left lower lobe contained more hæmorrhagic areas and firmer and more numerous areas of consolidation. The other organs of the body cavity showed no noteworthy abnormality.

On naked-eye examination the *brain* was tight within the dura mater. Slight creamy exudate was seen in the sulci in two places over the convexity of the left frontal lobe, and some creamy fluid in the lumbar sac. There was no other evidence of meningitis.

On section of the brain there was great congestion of the central white matter and of the central core of many of the convolutions with minute hæmorrhagic points. These were especially evident in the left frontal and parietal lobes and the central part of the corpus callosum. The left frontal lobe was slightly herniated across the mid-line over the corpus callosum. The congestion and haemorrhage were confined to the central regions of the brain, sparing the frontal, temporal and occipital poles. Although greater on the left side than the right it was of the same general character throughout. There was no special congestion of the cortex or basal ganglia. No macroscopic abnormality was seen in the brain-stem or spinal cord.

Histology.—What appeared to be the oldest lesions were in the corpus callosum where, in addition to congestion of vessels and many small hæmorrhages, there was loss of myelin round most of the vessels in more or less concentric zones, no wider than the diameter of small vessels (fig. 3A). In this zone and extending out considerably beyond it, but with no sharp line of demarcation, there was a great

increase in the number of nuclei, which were chiefly microglial, but the pyknotic remains of many polymorphonuclear leucocytes were also seen. Early fat phagocytes were present among the microglial cells, indeed most of the latter had a swollen, rather rounded cytoplasm. Round some vessels there were necrotic zones containing neither myelin nor cells, except very rare, irregularly shaped microglial nuclei. Many of the surrounding astrocytes had swollen or degenerated nuclei and the tissues appeared to be loosened by œdema. Many of the vessels in such areas had fibrinous exudate into and through their walls (fig. 3B).

A similar but less intense change was found in many parts of the frontal and parietal lobes. No lesions were seen in the frontal poles or the temporal or occipital lobes or basal ganglia. The cortex also was everywhere intact.

At the mid-level of the pons there was a sparse exudate of polymorphonuclear leucocytes round a few of the small vessels, with no other evident lesion. The cerebellum, medulla and spinal cord were normal.

Comment.—The case was regarded at first as one of hæmorrhagic influenzal encephalitis, a diagnosis in keeping with the terminology current at the end of the nineteenth century. Later, a comparison with the cases published by Weston Hurst and by Henson and Russell under the name *acute hæmorrhagic leuco-encephalitis* showed that this case was of similar type.

III.—Subacute Inclusion Body Encephalitis

Case 11.—M. R., female, aged 11. Duration of illness seven and a half months (indefinite symptoms), one month (definite symptoms). (Under the care of Dr. Grainger-Stewart at the National Hospital, Queen Square.)

History.—She used to be bright at school, but had learned less easily and had spoken less and less during the six to seven months prior to the onset of her fatal illness. On Christmas day 1942 she was unable to hang up her dressing gown as her hand was awkward, and she had difficulty in dressing herself. Later in the day she could not dance as her legs were awkward. She was noticed to be especially slow in answering questions. She was sleeping badly at this time. During the next fortnight she became very awkward in her movements, and rarely spoke or asked for anything and would not eat unless fed. There was nocturnal enuresis but she controlled her urine during the day. She appeared rather blind as she bumped into things unless guided ; she tended to drop things from her hands.

She was admitted to the National Hospital on January 7, 1943, where she appeared to be completely demented. She spoke very little either voluntarily or in answer to questions and appeared to understand little of what was said to her. She did, however, give her name "Maureen" but did not seem to know her surname. The pupils were large and reacted only slightly to light. The optic discs appeared normal. The blink reflex to light was absent in the right field of vision, although brisk in the left field, suggesting a right homonymous hemianopia. There was no apparent loss of power or inco-ordination of movement of the limbs nor any loss of sensation. The knee-jerks and ankle-jerks were more active than normal ; the plantar reflexes were flexor in type. She could stand alone but could not walk. The cerebrospinal fluid examined on January 12, 1943, was under a pressure of 175 mm. It contained 1 cell and 30 mg. protein per 100 ml., and gave a strong Lange reaction of paretic type 5554321000. The W.R. was negative in both blood and cerebrospinal fluid.

Her coma became rapidly deeper and she died on January 28, 1943. The temperature, which was normal on admission, rose on January 16 and remained irregular till her death.

Post-mortem examination showed no gross abnormality of the thoracico-abdominal organs.

Naked-eye examination of sections of the brain showed no abnormality of the cerebral hemispheres. In the pons there was, on one side, a cavity under the floor

of the fourth ventricle which involved the lateral two-thirds of the tegmentum extending forwards almost to the median fillet. It was separated from the wall of the ventricle by a thin neuroglial septum and was lined over most of its extent by ependyma and elsewhere by a flat cushion of neuroglial fibres. In one place it contained an included mass of neuroglial tissue with many calcified nodules of irregular shape near its margin. It appeared to be a congenital malformation of the nature of a syringo-pontis. No secondary degeneration of the inferior olives was present.

Histology.—Sections of the cerebral cortex and white matter showed a varying degree of subacute inflammatory change, consisting of increase in number and size of microglial nuclei, perivascular infiltration with lymphocytes and plasma cells, evidence of cell division and hyperplasia in the astrocytes, and in some areas degeneration of isolated cortical neurons with intranuclear and cytoplasmic inclusion bodies in a few of these.

The *left occipital lobe* was most affected. Here some areas showed severe perivascular infiltrations with lymphocytes and plasma cells, and very evident increase both in size and number of microglial nuclei, with many rod cells orientated at right-angles to the surface. In the astrocytes there were both signs of nuclear division, such as pairs and quadruplets of nuclei, and swelling of the cell body with early fibre formation especially in the second and fourth layers.

In the most affected areas there was considerable loss of neurons, and occasional degenerated cells were seen, some of which contained hyaline intranuclear inclusions, some small and surrounded by a definite halo, others filling the nucleus more completely. An occasional very degenerated cell, with its cytoplasm almost entirely replaced by inclusion body material, was also seen. In the underlying white matter the astrocytes had swollen cell fibres. Many vessels were cuffed with lymphocytes and plasma cells, which also lay free in the tissues. There was also considerable excess of microglial cells. In sections stained with scarlach R and hæmatoxylin, areas were found in the parietal lobes where myelinated fibres entering the deeper cortical layers were greatly reduced in number, and sudanophil lipoid was present in many swollen microglial cells. The white matter immediately under these areas, although still containing many intact myelin sheaths showed numerous fat granule cells of more rounded shape than those in the cortex.

The *hippocampus* was very little affected. An occasional cuffed vessel and a few glial stars were seen, and a very occasional neuron of the pyramidal layer was degenerated. No inclusion bodies were found here. There was slight gliosis, especially in the bight of the fascia dentata.

In the *basal ganglia* similar slight inflammatory changes were seen, no more in one nucleus than in another. A few astrocytes in the centre of the putamen had formed fibres.

In the *mid-brain* and *pons* an occasional glial star and a few infiltrated vessels were seen in the tegmentum, and among the nuclei pontis, where the microglial excess was also more diffuse. Similarly the *Nucleus dentatus* showed a rather diffuse increase of microglia. Neuronophagy of one cell was seen here and an occasional plasma cell was found near a vessel.

In the *medulla* a few glial stars were seen in the olives. The more dorsal areas of the medulla and the cerebellar cortex were free from lesions.

Subacute Inclusion Body Encephalitis

Case 12.—B. H., male, aged 9 years. Duration of illness five and a half months. (Under the care of Sir Charles Symonds at Guy's Hospital and the National Hospital, Queen Square.)

History.—At the age of 7 years he had an attack of cerebrospinal meningitis, in which he was in coma, but he recovered completely from this. Three weeks before the onset of the fatal illness he had an attack of rubella. About the beginning of

May 1947 he began to drop things from his hands, apparently owing to shuddering movements which affected the whole body and occurred every half-hour or so. After a few days these movements became more frequent and after a week they recurred every five minutes. He was put to bed and after this, when he tried to stand, his legs seemed too weak to support him. After nine weeks illness' he was admitted to Guy's Hospital on July 8, 1947, under the care of Sir Charles Symonds. There it was noted that he was slow to understand what was said to him and there was perseveration of speech and action. Occasional twitching movements in the forearms and hands and symmetrical weakness of the lower facial muscles were also present. When he protruded his tongue irregular movements were seen in it. All the limbs were rather rigid ; the plantar reflexes were of flexor type. While in hospital his condition steadily deteriorated. He appeared to take little interest in his surroundings and frequent spasms, with arching of the back, set in.

On July 23 he had a fit, lasting for half a minute with clonic movements of the right arm and leg and the abdominal musculature. He appeared to be conscious during the fit, and after it the right limbs were extended, the left flexed, and the right plantar reflex was extensor in type.

He was transferred to the National Hospital on August 26. On examination there he appeared to be conscious of his surroundings. He tried to obey simple commands and sometimes spoke if spoken to, but did not answer questions. He groaned constantly and any sudden noise made him jump violently as if he were terrified. There was a constant *risus sardonicus*. Apart from the spasms, described below, there was no stiffness of the neck. He followed a moving object with his eyes and there was no nystagmus. The plantar reflexes were flexor.

Every ten minutes or so he went through a cycle of involuntary movements which consisted of (1) a relaxation of rigidity followed by a jerky spasm of one or both arms or slight flexion of the knees, (2) full extension of the spine going on to opisthotonus ; the legs and arms went into extensor spasms ; supination was followed by hyperpronation. The right arm at this stage might be semi-clenched at the elbow. During these movements conjugate movement of the eyes to the left was relaxed and the eyes returned to the central position. Under treatment these spasms improved somewhat for a time.

On September 1 lumbar puncture gave C.S. fluid under a pressure of 200 mm. It contained 1 cell per c.mm. and 20 mg. protein per 100 ml. and gave a weak Lange reaction in the paretic zone, 2211000000.

On September 4 a biopsy of the brain was made through a right frontal burr hole. Histology of the tissue removed showed evidence of subacute encephalitis, but no inclusion bodies were seen. The remainder of the tissue was sent to Professor S. P. Bedson who inoculated it into animals, but with negative results.

By September 20 the boy's condition had become worse. He was very wasted ; the spasms and rigidity had returned and there was seldom any relaxation. He died on October 16, 1947.

Several electro-encephalographic examinations were made during his stay in hospital. These are being reported, along with those of other similar cases, in a separate article by Drs. Dennis Hill and W. A. Cobb.

A *post-mortem* examination was made fourteen hours after death. Apart from the burr hole in the right frontal region there was no external evidence of disease. The brain showed no naked-eye abnormality except some plastic thickening of the pia-arachnoid in the region of the cisterna magna and covering the inferior medullary velum, so that no foramen of Magendie could be made out. There was, however, no hydrocephalus. This was considered to be the result of the previous meningitis.

The brain did not feel abnormally firm. It weighed 1,400 grammes. Some nodular bronchopneumonic patches were found in the outer part of the lower lobe of the left lung apparently secondary to collapse of this area. More superficial collapse was seen at the outer part of the right base. The outer organs of the body cavity were normal.

Histology of the brain.—Subacute inflammatory changes were scattered very widely through the cortex, less in the Rolandic cortex than in many other areas, and greatest in the right temporal and occipital cortex. Where most intense there was hyperplasia and increase in number of microglial nuclei, fairly heavy perivascular infiltration and some lymphocytic infiltration of the meninges. Many of the cortical neurons were irregularly shrunken and an occasional figure of neuronophagy was seen. There were also glial stars not apparently related to nerve cells especially in the deeper cortical layers. Astrocytic proliferation was shown by the presence of many pairs and a few clusters of four nuclei, and some fibrous gliosis was present in the fifth and sixth cortical layers. The myelin in the subcortical white matter was fairly well preserved, but in some areas, just under the cortex of the frontal lobes as well as further back, there was a diffuse powdering with sudanophil granules, which had not progressed to the formation of fat granule cells, except in the walls of the vessels. In the cortex also granules of sudanophil material were seen in the processes of the microglial cells, especially in the first and third to sixth layers.

Where the inflammatory reactions were most intense a few neurons contained intra-nuclear and intra-cytoplasmic inclusion bodies. They were fairly abundant in some areas, as many as six such neurons being present in one high-power field. A few oligodendroglial nuclei also were almost filled by inclusions.

In the *left hippocampus* there was an almost total loss of pyramidal cells in Sommer's sector under the wall of the ventricle in the more anterior part of this formation. This layer was replaced by swollen bodied astrocytes and microglia. There was no inflammatory reaction in this area.

The *basal ganglia* showed only slight and scattered lesions. In the *putamen, caudate nucleus* and *globus pallidus* none were found. In the *thalamus* there were occasional foci of microglial proliferation and slight cuffing of vessels with lymphocytes and plasma cells. A few vessels contained recent, probably agonal thrombi. In the *mid-brain, pons* and *upper medulla* a few glial stars and infiltrated vessels were seen, but the changes were slight.

In the *cerebellar vermis* and *tonsils* many convolutions at or near their summits contained small areas of cortical shrinkage with slight to great loss of granule cells and some loss of Purkinje cells. There was a varying degree of isomorphic gliosis of the molecular layer. No perivascular infiltration or other evidence of inflammation were seen in these areas, and in some the gliosis was so intense as to suggest that the degeneration antedated the final illness. Like the plastic meningitis in this region it was probably related to the previous attack of meningitis.

Subacute Inclusion Body Encephalitis

Case 13.—S. C., female, aged 9. Duration of illness four-and-a-half months. (Under the care of Dr. M. J. McArdle at the National Hospital, Queen Square.)

History.—She was a normal healthy child till the onset of the fatal illness. The first symptom, about three months before admission to hospital, was enuresis. A week later her mother noticed that she was falling about. Once she fell in the bathroom where her mother, a few seconds later, found her dazed but not unconscious. During the next fortnight she was listless and seemed tired. When sent out on a small errand she did not return and her mother found her wandering aimlessly about. She sometimes talked nonsense without realizing it and her voice became toneless. A fortnight later she seemed to lose control of her hands ; there was a difficulty in initiating the movement as well as clumsiness. She was admitted to Queen Elizabeth's Hospital for Children on October 2, and was there for six weeks. On October 7 an irregular tremor developed in the tongue and fingers. By October 11 she had become more unsteady on her feet and she complained of visual hallucinations. By the end of October she had become drowsy and disinclined to move and since then steady deterioration had set in. The face and limbs were spastic and she drooled at the mouth.

On November 1 the C.S. fluid contained 1 cell. Protein 30 mg. per cent. NaCl 765 mg. per cent. Glucose 86 mg. per cent. and gave a paretic Lange reaction (4321000000).

On November 13, while still normal otherwise, it gave a similar Lange reaction (3321000000).

On November 11 and 12 various biochemical investigations were made with normal results. (Thymol turbidity 4 units. Alkaline phosphatase 4·8 units. Serum bilirubin 0·5 mg. per cent. Serum calcium 11·4 mg. Serum NaCl 578 mg.)

She was transferred to the National Hospital, Queen Square, on December 15, 1948. There she lay with her lower jaw rigidly open and her tongue protruding slightly to the left. She was mute but later on made a whining sound. She followed the examiner with her eyes and blinked if threatened. She occasionally smiled in a slow plastic fashion, but her face was usually expressionless. She lay on her right side with the thighs and knees flexed into the abdomen. The left arm was flexed and adducted, the wrist and fingers flexed. The right arm was abducted at the shoulder, flexed at the elbow and dorsiflexed at the wrist. The thumb was kept in the mouth. The whole limb trembled rhythmically in this position. Every now and again she passed the right hand six inches in front of her face as though warding off a blow and while doing so there were repeated sudden jerks of adduction of the limb, again as though she expected to be hit. In addition she was subject to sudden rapid spasms involving all her musculature. The impression was that she gave a sudden start to prevent herself from falling through the bed. The spasms consisted of sudden flexion of the trunk and neck, flexion of the knees and hips and extension of the arm forwards. They occurred every two to three minutes, and during them she usually closed her eyes and screwed up her forehead. They were not initiated by noises or by jarring the bed. She was incontinent of urine and faeces, and did not respond to any command. She was able to swallow but unable to open her mouth sufficiently to allow a spoon to be inserted between the teeth. The pupils reacted well and the external ocular movements were full. The optic discs appeared pale. She resented painful stimuli everywhere. There was generalized plastic rigidity of all the limb muscles, more on the left than the right, and especially affecting the flexion of the elbows and the hamstrings. This rigidity fluctuated but was never absent, and was sometimes so strong that the limb could not be straightened, but there was no contracture. Power appeared to be well preserved at all joints. The deep reflexes were present ; the plantars extensor in type.

On January 13 a biopsy of brain was made by Mr. McKissock. This confirmed the diagnosis of subacute encephalitis, but the type could not be distinguished.

By January 20 she lay in a position of severe opisthotonus. The myoclonic jerkings were now less frequent and were confined to the upper shoulder. By January 25, they had almost entirely disappeared. (Several electro-encephalographic examinations were made by Dr. Cobb, and are being reported in the article already referred to.)

She died on January 31, 1949, and a post-mortem examination was made nine hours later. The right lung was congested and œdematous in all its lobes, with small foci of early bronchopneumonic consolidation. The other organs of the body cavity appeared healthy.

The *brain* appeared normal with rather more hollowing of sulci than is normal for this age. The arteries were healthy. The brain tissue was firm and retained its shape when cut in the unfixed state. There was no dilatation of ventricles. Large frozen sections of the frontal lobes showed no direct evidence of demyelination, though an occasional vessel in the white matter of the convolutions had a ring of fat granule cells round it. (This may be normal at this age.) A larger number of vessels in the white matter were cuffed with lymphocytes. Throughout the cortex an occasional cuffed vessel was seen and there was a focal increase of microglial nuclei. Most of the nerve cells were normal except in the frontal lobes, and especially

in the frontal operculum of the island of Reil. Here areas of more intense microglial hyperplasia and proliferation were present, and many of the vessels were heavily cuffed with lymphocytes and rarer plasma cells which also lay free in the tissues. Several of the pyramidal nerve cells in these areas contained intranuclear inclusions (fig. 4). These were nowhere abundant and cytoplasmic inclusions were difficult to recognize but in some severely degenerated nerve cells the cytoplasm had assumed the same hyaline appearance as the inclusions. Some intranuclear inclusions were half as wide as the nucleus, and were surrounded by an unstained halo, but most were smaller and only an occasional inclusion body filled the nucleus completely. In some cells as many as three intranuclear inclusions could be seen. In such cells the cytoplasm was always degenerated and often shrunken and eosinophilic. Nowhere could more than four cells with inclusions be found in one high power (4 mm. obj.) field and in many areas it was necessary to search many fields before finding any, but prolonged search revealed occasional inclusion bodies in most cortical areas.

In sections stained by Cajal's gold sublimate method, definite hyperplasia of astrocytes was seen in most areas, with abundant pairs in mirror image and some quadruplets.

In the white matter the cell bodies of the astrocytes were somewhat swollen but there was less evidence of proliferation and none of myelin katabolism.

In the *putamen* and *nucleus caudatus* there was microglial hyperplasia and an occasional glial star. Pairs of astrocyte nuclei were common. An occasional degenerated nerve cell was seen but none contained inclusion bodies. There was no perivascular infiltration here. No lesions were found in the *globus pallidus*. Rather more microglial proliferation was seen in the thalamus. Here it was chiefly diffuse, but many loose aggregations of microglial nuclei were seen. There was no fibrous gliosis. The neurons were little affected. Perivascular infiltration was here quite slight.

In the *nuclei pontis* there were in some places fairly dense collections of microglial cells and a few intranuclear inclusions were seen in the nerve cells. Similar microglial collections were seen in the *inferior olives* and *dentate nucleus* of the cerebellum. The cerebellar cortex and spinal cord showed no lesions. No iron was found in sections with the Prussian blue method except along the line of the biopsy wound.

Subacute Sclerosing Encephalitis

Case 14.—M. D., female, aged 20. Duration of illness six months. (Brain received from Dr. Hugh Garland of Leeds.)

History.—The patient appears to have always been rather backward at school, and on leaving school got rather out of hand. At the age of 17 she developed vulvar warts, but there was no other evidence of venereal disease.

In July 1947 she was admitted to Leeds General Infirmary for the surgical treatment of the warts, but owing to the development of other symptoms this was put off. About this time weakness of the left arm was noticed, and she had obviously regressed mentally, being in a condition resembling hysterical stupor. In the course of the next month or so the left arm became paralysed. She was transferred to St. James' Hospital on November 12, 1947, as she could not walk, and at this time it was noted that there was complete lack of facial expression, the mouth remaining constantly open and speech being monosyllabic ; she talked a little to her mother, but her speech was very dysarthric. At this time she could feed herself with her right hand. Early in December she became doubly incontinent and by this time was lying in bed with both legs flexed at the hips and knees. All the limbs were extremely rigid. She had considerable pyrexia attributed to cystitis and grossly infected vulvar warts.

Dr. Garland saw her in December. There was then almost total paralysis of all four limbs which were flexed at most joints and very rigid. The face was that of

a very advanced Parkinsonian, the mouth always open and speech limited to unintelligible grunts ; the pupils were sometimes widely dilated, though always reacting. There were no sensory changes or unequivocal pyramidal signs. During the remainder of her life there was almost complete absence of voluntary movement, with the exception of an occasional eye movement. At the same time, almost up till the time of death at the end of January 1948, she seemed to understand what was being said to her.

The cerebrospinal fluid, examined on November 15 and again on November 22, contained no cells, and normal protein (16 and 10 mg. per 100 ml.), but gave Lange reactions of paretic type (543320000 and 4221100000).

Post-mortem examination.—The brain on section showed no naked-eye abnormality.

Histology.—Throughout the *cerebral cortex* of the frontal, temporal and occipital lobes there was everywhere hyperplasia, with little increase in numbers of microglial nuclei. Proliferation of astrocytes with many pairs and quadruplets of nuclei was also seen ; the cell body was not enlarged and fibres were only found in relation to medium-sized vessels. Many of the latter had a single, often incomplete ring of plasma cells in their walls and lymphocytic infiltration was seen round the meningeal vessels. The cortical neurons showed little abnormality, only an occasional cell having a rather ragged cytoplasm and diffusely stained nucleus. No inclusion bodies could be found.

The lesions in the white matter were more severe, especially in the upper frontal and occipital regions. In sections stained by scharlach R and hæmalum there was here slight rarefaction of myelinated fibres and a diffuse scattering of fat granule cells (fig. 5A). Much of the contained lipoid was anisotropic, some transmitting white light under crossed Nicol prisms (probably cholesterol crystals). These areas stained rather less deeply than the surrounding white matter with hæmatoxylin stains for myelin, but there was no gross demyelination.

In celloidin sections of these areas of white matter there was a diffuse excess of microglial nuclei, diffusely scattered or forming small rosettes. Plasma cells, many of which had two or more nuclei, infiltrated the walls of the vessels and were sparsely scattered in the tissues. An occasional " Russell body " was seen close to a vessel. Many of the nuclei of the astrocytes were swollen and their cell body just visible. Definite increase of neuroglial fibres was present (fig. 5B).

In the *hippocampus* the lesions were minimal ; only an occasional degenerated neuron and slight focal excess of microglia were seen here. The *thalamus* also contained areas of microglial proliferation and an occasional cuffed vessel. The *putamen*, *globus pallidus* and *nucleus caudatus* were normal except for an occasional glial star and infiltrated vessel. The *substantia nigra* was affected to a similar extent, the pigmented nerve cells here being quite normal.

In one *inferior colliculus* there was glial scarring round dilated vessels, and at this level the median V of the fourth ventricle was filled up by neuroglial overgrowth. At the level of the pons also there were a few sub-ependymal glial tufts and a focal and diffuse excess of microglial cells among the nuclei pontis. Perivascular infiltration of a few vessels and slight meningeal infiltration were also present at this level.

In the *nucleus dentatus* and *inferior olives*, as well as under the floor of the fourth ventricle in the medulla, there were fairly large microglial accumulations. A very few small ependymal granulations were seen in the lateral recesses of the ventricle ; none was seen in the more central parts of the floor of the ventricle. The *cerebellum* and *lower medulla* were free from lesions.

VISUAL-SPATIAL AGNOSIA ASSOCIATED WITH LESIONS OF THE RIGHT CEREBRAL HEMISPHERE

BY

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I. Introduction

Two cases of visual-spatial agnosia associated with traumatic lesions of the right cerebral hemisphere were reported by Paterson and Zangwill in 1944. In these cases pronounced defects were observed in the analysis of spatial relationships and in the execution of constructional tasks under visual control. The disability was particularly marked in tasks which demanded a fine appreciation of spatial structure, e.g. in drawing, copying and assembling mosaic patterns. It was also noted that characteristic anomalies of oculomotor control were present in both cases and a peculiar lability of fixation in one. These symptoms, it was argued, exacerbated the perceptual disability but could not with propriety be regarded as its cause. A third case of the same general type was reported by the same authors in a later paper (Paterson and Zangwill, 1945). In this case, however, oculomotor disabilities were negligible or absent and an additional and severe disorder of topographical memory was in evidence. Although the lesion in all three of their cases was right-sided, Paterson and Zangwill drew attention to the somewhat similar patterns of disability which had been recorded in cases with broadly comparable lesions of the left cerebral hemisphere, e.g. those of Head (1926) and Poetzl (1928). It was concluded, therefore, that further research was demanded before the respective significance of the major and minor hemisphere for visual-spatial cognition could be defined with any precision.

A number of cases displaying visual symptoms closely parallel to those described by Paterson and Zangwill (1944, 1945) have since been reported in the literature. Lenz (1944) has called attention to a systematic deformation of the visual co-ordinates associated with circumscribed occipito-parietal lesions of the right cerebral hemisphere. In a series of 56 cases of brain injury, 6 were found to present a peculiar pattern of visual disorientation. In these cases, consistent errors were made when the patient was required to place a rod in the vertical or horizontal position or to indicate the main directions of space by drawing. "The

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characteristic symptom was the inclination of the horizontal and the vertical towards each other, thus forming an oblique angle, i.e. a distorted system of co-ordinates " (Lenz, 1944, p. 45). These errors, it was found, could be markedly accentuated by freezing a small area of scalp overlying the bone defect by means of an ethyl chloride spray—a technique ascribed to Trendelenburg. Lenz found that the lesion in all 6 cases presenting this disorientation involved the occipito-parietal region of the minor hemisphere and that no comparable disturbance was in evidence in cases with broadly corresponding lesions of the major hemisphere. He was therefore led to conclude that the findings " . . . demonstrate the great importance of the right parieto-occipital cortical area for all directional operations in visual and sensorimotor space " (Lenz, 1944, p. 63).

A more extensive investigation of the visual co-ordinate system has recently been reported by M. Bender and R. Jung (1948). In a systematic study of 100 cases of brain injury, these authors report varying degrees of deformation of the co-ordinates in patients with unilateral lesions of either hemisphere. They state that the direction and extent of deformation varied simply with the laterality of the lesion ; deviations in right-sided cases were in an anti-clockwise direction, from the patient's point of view ; in cases with left-sided lesions, they were in an opposite direction. As regards magnitude, the authors are led to conclude that " . . . right-sided cerebral injuries give rise to more marked deviations of the subjective vertical and horizontal than do comparable injuries of the left side " (1948, p. 204).

Statistical examination of the data presented by Bender and Jung indicates on the one hand that, considering *laterality alone*, only the deviations recorded in right-sided cases are significantly different from those in normal subjects. More detailed analysis, on the other hand, reveals that their conclusion with regard to laterality is valid if *only* frontal and parietal lesions are considered : in cases with temporal and occipital lesions the deviations are significantly greater than in normals only for cases with left-sided lesions, and in these cases the direction of the deviation is anticlockwise.

It would appear, then, that some degree of distortion of the visual co-ordinates may be found with a wide range of unilateral cerebral injuries and cannot be regarded as a focal sign of occipito-parietal damage. It is noteworthy, however, that the deformation is typically more extreme in cases of right-sided injury. Bender and Jung do not comment upon any other aspect of visual-spatial disturbance exhibited in their material.

An experimental study of visual disorganization following cerebral injury has recently been communicated by M. B. Bender and H. L. Teuber (1947, 1948). The main object of this study was to define with greater precision the nature of visual perception in hemi-amblyopic fields, with special reference to the phenomenon of unilateral visual disorientation first described by Riddoch (1935). Detailed investigations are reported in 2 cases, in both of which the lesion was right-sided. In the first, the fronto-parietal region was involved, in the second, the occipital

lobe and the posterior portion of the parietal lobe. Both patients presented characteristic defects of visual localization in the affected parts of the visual field. In particular, the findings suggested a systematic deformation of the visual co-ordinates and partial rotation of the entire subjective coronal plane. In the sagittal plane, there was a marked degree of teleopsia associated with peculiar changes in the apparent size and shape of perceived objects. These defects, it must be stressed, were peculiar to the affected portions of the visual field and are presumably unaffected by the laterality of the lesion.

Bender and Teuber call attention to some further aspects of visual-spatial disorganization exhibited by their patients. The first patient, while showing slight visual-constructive defects on special tests, gave no evidence of topographical disorientation. The second patient also showed a gross disturbance on constructional tasks and his drawings were marked by a singular lack of perspective. In plan drawing, there was a slight, though significant, want of coherence : " He did not seem able to use salient features of the route as points of reference or landmarks " (Bender and Teuber, 1948, p. 51). But it is noteworthy that the patient displayed no appreciable defect in finding his way about in familiar surroundings. In this case, then, as in those described by Paterson and Zangwill (1944), we find a pronounced impairment of visual-spatial cognition without manifest topographical disorientation.

The disorder known as " apraxia for dressing " (Russell Brain, 1941) is commonly encountered in cases with visual-spatial disabilities of the type described. It was strikingly apparent in the case of topographical memory loss reported by Paterson and Zangwill (1945). Hécaen and Ajuriaguerra (1942–5), in a systematic study of this disability, comment on its close relationship to disorders in the visual-spatial sphere. Of the 5 original cases which they report, it is of some interest to note that the responsible lesion was almost certainly right-sided in 4 cases and left-sided in only 1. These authors further point out that in 10 cases showing dressing disorders reported in earlier literature, the lesion was definitely right-sided in 5 cases and probably right-sided in 1. In only 1 case (Russell Brain, 1941) was the lesion unequivocally left-sided. This predominance of right hemisphere lesions in relation to visual-spatial and kindred disorders, which was recognized earlier by Dide (1938), will be considered in greater detail below. We may note in passing, however, that Roth (1949), in a recent study of anosognosia, reports " apraxia for dressing " and failure on constructional tests in 2 cases with massive lesions of the right parietal lobe.

The general outcome of these more recent investigations is to suggest that disorders of visual space perception, although liable to accompany unilateral lesions on either side, are especially prominent in cases with involvement of the posterior parts of the right hemisphere. This would appear to conflict with the generally accepted view that spatial disorientation and kindred symptoms are to be ascribed to a lesion of the

dominant hemisphere (Russell Brain, 1945 ; Nielsen, 1946 ; Duke-Elder, 1949 ; Hécaen and Ajuriaguerra, 1949). The evidence, however, appears to be far from conclusive. Although there can be no doubt that defects of visual-spatial cognition are present in many cases of left-sided cerebral lesion in right-handed individuals, the majority of cases in which massive loss of topographical orientation has been reported are either cases in which the lesion was bilateral (Holmes, 1918 ; Hécaen and Ajuriaguerra, 1949) or cases in which the lesion was limited to the right cerebral hemisphere (Hughlings Jackson, 1876 ; Russell Brain, 1941 ; Paterson and Zangwill, 1945). Nielsen, it is true, ascribes spatial disorientation to a lesion affecting the occipital lobe of the major hemisphere. But it is notable that in a case presenting this symptom which he himself reports (1946, pp. 203–5), the lesion was located in the right occipital lobe. Pfeffer, Friedman and Wortis (1946) likewise ascribe this feature to a lesion of the left occipital or occipito-parietal area. In their case, however, the lesion was almost certainly bilateral and its value as evidence correspondingly reduced. Hécaen and Ajuriaguerra (1949, pp. 301–2), although maintaining that the left hemisphere is dominant with regard to topographical memory, nevertheless comment on the occurrence of disorders in this function in cases with unilateral lesions of the right occipito-temporal cortex. Although it is possible, as Russell Brain (1945) and others have argued, that the hemisphere dominant for handedness and speech may not necessarily be dominant for spatial orientation, it is at all events surprising to note the frequency of topographical disorientation and memory loss in cases with lesions limited to the right cerebral hemisphere.[1]

In view of the prevailing confusion regarding the respective significance of the major and minor hemisphere in relation to spatial organization, it is felt that well-controlled studies of patients with broadly comparable left-sided and right-sided occipito-parietal lesions are urgently required. To this end, we shall communicate in the present paper a series of 8 cases presenting in marked degree the pattern of visual-spatial agnosia as described by Paterson and Zangwill (1944, 1945). This disability, which has been termed " apractognosia for spatial articulation " in the German literature (cf. Lange, 1936), is closely related to, if not identical with, the syndrome described by Marie, Bouttier and Bailey (1922) under the name of *planotopokinesia*. In certain of our cases, the visual-

[1]It must of course be borne in mind that disturbances of topographical orientation, as Russell Brain (1941) has insisted, may issue from a number of more specific causal factors. Not uncommonly, loss of topographical orientation can be traced to massive neglect of the left half of visual space—a disability to which Duke-Elder (1949) has given the name of *unilateral spatial agnosia*. This symptom, which is often prominent in cases with extensive right parietal lesions, undoubtedly accounts for the greater part of the topographical disability observed by Russell Brain (1941) in his own cases and in those of Roth (1949). In other cases, however, as in those of Meyer (1900) and Paterson and Zangwill (1945), it appears necessary to postulate an additional and specific defect of topographical memory.

spatial impairment was associated with marked disturbance of topographical orientation and memory and an attempt will be made to analyse in some detail the origins of this disturbance. The location of the lesion was exclusively (or predominantly) right-sided in all cases and in no patient was there evidence either of dysphasia or left-handedness. It may therefore be assumed with some confidence that the minor hemisphere (as ordinarily defined) was predominantly involved. The aim of the present study is first, to define the syndrome of visual-spatial agnosia with greater precision, paying particular regard to the presence or absence of oculomotor defects and of wider topographical disturbances; and second, to elucidate further the nature of the disability in its psychological aspects. It is also hoped that the evidence we shall present regarding the location of the lesions in this series of cases will be of value from the standpoint of comparative study. A parallel series of cases with broadly comparable lesions of the left hemisphere will be communicated at a later date.

II. Cases

Case 1.—A skilled fitter, aged 49, was admitted complaining of progressive loss of usefulness of the left hand and a tendency to lose his way in familiar surroundings.

Five months previously the patient dropped a piece of metal from his left hand and since then this hand had become weaker and the fingers invaded by a tingling sensation. He often dropped implements held in this hand and two months later dropped his watchmaker's glass from the left eye. One month later, he began to lose his way home from work. Blue-prints became confusing and in reading he found himself missing lines. At this time he first noticed difficulty in dressing, often putting on his clothes back to front. He noticed some inability to see out of the corner of his eye, particularly on the left, and began to forget where he had put things. On occasion, he was more short-tempered than usual. He had tended to become more untidy in the month preceding admission and his appetite increased a little. Two weeks later, he began to have frontal headaches. There was no difficulty in walking, no sphincter disturbances and no episodes of loss of consciousness.

On *neurological examination* the patient was found to have a left homonymous hemianopia, sparing the macula. Fundi normal. There was moderate upper and lower left facial weakness, more marked on voluntary movement. The left arm was spastic, the left wrist weak, and co-ordination and fine repetitive movements impaired. There was also slight hypertonus in right elbow and shoulder. Both legs were spastic, more so on the left, without weakness. Tendon reflexes were bilaterally hyperactive, more so on the left; abdominals present; left plantar extensor. Pain, temperature and vibration were normally perceived; touch slightly impaired on left hand and occasional extinction to touch on whole left side. Two-point discrimination and joint position sense were impaired in the left arm and leg. No apraxia apart from constructional defects described below.

On *psychological examination* the patient's pre-morbid intelligence was placed in the high-normal range and there were indications of only very mild general intellectual impairment. Vocabulary (Terman-Merrill): Score—31. No dysphasia, no defects of oral comprehension or of interpreting pictures. No abstraction defect on Weigl's sorting test. No finger agnosia and discrimination of left and right correct on his own body.

There was marked disability on all psychometric tests involving *visual-spatial relationships*. Progressive matrices (Raven, 1938): Score—12/60. He could do

only the first of Kohs' Block Designs. He was able to copy only the simplest patterns and drawings from memory were extremely poor, and he was unable to draw a rough map of England or a ground-plan of his house. Memory for events, on the other hand, was intact. There was massive neglect of the left half of visual space (unilateral spatial agnosia of Duke-Elder, 1949). The patient consistently neglected the left side of a picture or line of print. But he was able to count scattered pins or coins and to estimate correctly the distance of objects in the central field of vision. There was some difficulty in left-right orientation in regard to other persons or external objects. There were no gross personality changes: insight was fair but the patient was unable to appreciate his errors in the visual-spatial sphere.

Three weeks after admission, the patient suddenly developed an almost complete left hemiplegia. From this he was slowly recovering when, four months later, he died following a superior mesenteric thrombosis.

On *post-mortem examination* there were thromboses in many other arteries, including the right internal carotid. In the brain, there was on the left side a pale opacity of a small surface artery and a scarred depression for 5 mm. round it on the surface of the upper part of the convexity of the occipital lobe. On the right side, there was an old infarction of grey and white matter extending from the cortical surfaces of the superior and middle frontal gyri, posteriorly to the convexity of the occipital lobe and inferiorly to the middle temporal gyrus. Deeply, the supero-lateral quadrant of the corpus striatum, all the lentiform and the body of the caudate nucleus were involved (fig. 1A).

The main features of psychological interest in this case are (1) Massive neglect of the left side of visual space (unilateral spatial agnosia); (2) gross visual-constructive disabilities on special tests; (3) apraxia for dressing, and (4) episodes of topographical disorientation in familiar surroundings. In view of the fact that a further vascular catastrophe took place three weeks after admission, it may be presumed that these defects were associated with a right-sided cerebral lesion somewhat more restricted than that defined post mortem.

Case 2.—A housewife, aged 65, was admitted complaining of headaches and visual disturbance, and with a history of difficulty in finding her way about.

One year previously she began to have occipital headaches and noticed that she could not see very well to the left and had difficulty in judging distances in that direction. She began to leave food on the left side of her plate or to push it off on to the table. In reading, she experienced difficulty in shifting down to the next line. About the same time, she began to have great difficulty in finding her way about in places she knew well. This improved slightly but the patient noticed great difficulty in learning her way around in a strange house. Also, on standing up, it took her a few moments to "get her balance."

On *neurological examination* she displayed a complete left homonymous hemianopia to confrontation. Visual acuity 6/9 in both eyes. Bilateral blurring of the nasal margins of the optic discs. Slight weakness of emotional expression on the left. In walking, her gait was unsteady. She tended to veer to the left and occasionally collided with objects on this side. The arms were normal. The left leg was weak, especially in hip and knee joints, and co-ordination of movement in this limb was slightly impaired. Tendon reflexes were brisker in the left leg; abdominals were present and the left plantar response extensor. Pain and temperature were appreciated normally but light touch missed on the left leg and there was extinction on the left arm and leg to bilateral touch. Joint position sense was impaired on the left; two-point discrimination was impaired on the left hand and lips and stereognosis very occasionally inaccurate in the left hand. Pointing

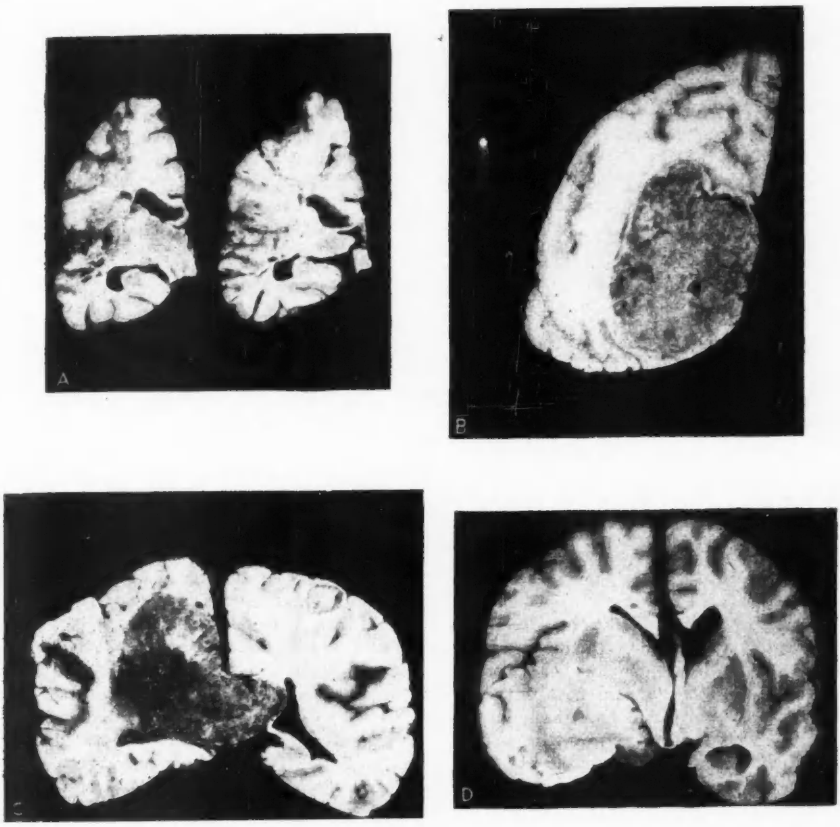

FIG. 1.—*Photographs of sections of right cerebral hemispheres.* A. Case 1. B. Case 2. C. Case 4. D. Case 5.

to objects in the visual field was better to her right than to her left irrespective of the arm used. There was no apraxia, except in the constructional sphere and for dressing.

On *psychological examination* pre-morbid intelligence was placed in the low-normal range. Vocabulary (Terman-Merrill): Score—24. Mild non-specific intellectual impairment on special tests: Unable to learn Babcock sentence or to execute Weigl's sorting test adequately. No dysphasia or kindred disorder of language and no left-right disorientation on herself or examiner. Apraxia for dressing was revealed in confusion in putting on her dressing-gown, both as regards top and bottom and back and front of the garment.

Gross defects were present in the *visual-spatial* sphere: Progressive matrices (Raven, 1938): Score—10/60. She was unable to perform any of Kohs' Block Designs or to copy simple designs with pencil or matchsticks. She was unable to sketch a rough map of England or to locate large towns on a presented map. In trying to learn her way about the hospital, she was observed on occasion to miss turns to the right as well as to the left.

There was no gross personality change. The patient was not amnesic and was well oriented socially, but had no insight into her specific disabilities. She gradually deteriorated, becoming confused, deluded and hallucinated, and finally stuporose. Death took place three months after admission.

On *post-mortem examination* there was in the brain a papilloma of the choroid plexus on the right, coming to the surface in the region of the calcarine fissure. It occupied more than a quarter of the cross section of the right occipital lobe, just behind the lateral ventricle (i.e. the inner two-thirds of its transverse diameter and the lower two-thirds of its vertical diameter) and it came to the surface over half its medial surface and the inner third of its lower surface. It thus destroyed the calcarine region except at its tip (fig. 1B).

The salient disabilities in this case are (1) Massive unilateral agnosia for the left side of visual space; (2) gross visual-constructive defects; (3) impairment of topographical orientation; and (4) mild apraxia for dressing. These disabilities were associated with an extensive space-occupying lesion involving the medial two-thirds of the right occipital lobe.

Case 3.—A master printer, aged 55, was admitted complaining of weakness of the left arm and leg and with a history of visual-spatial disturbances.

Six weeks previously, the newspaper in his hands suddenly appeared to swing round to the right; he became dizzy and collided with objects to his left. An hour or so later he lost consciousness but it was restored after a short interval.

Two weeks later, his wife noticed that the patient placed the knives and forks on the table with their upper ends tilted to the left and that he kept shifting his plate towards his left-hand side. On the following day, without loss of consciousness, his left arm and leg became suddenly weak and numb. He also noticed some impairment of memory and, in typing, he would omit the spacing between the words.

On *neurological examination* there was a left homonymous hemianopia up to 10 degrees left of the fixation point. V.A.R.—6/9; V.A.L.—6/12. Fundi normal. Left arm and leg were slightly spastic, and weak, and co-ordination impaired in both. Exaggerated associated movements in left hand. Tendon reflexes exaggerated on left; abdominals absent on left; left plantar response extensor. Pain and temperature sensation normal. Joint position sense grossly defective in left arm and leg and two-point discrimination and stereognosis impaired also. Extinction on left of bilateral pin-prick on hands.

On *psychological examination* pre-morbid intelligence was placed in high-normal range. Vocabulary (Wechsler-Bellevue); Score—33. No psychometric evidence of general intellectual loss or verbal learning defect. Calculation was unimpaired.

No evidence of dysphasia and no comprehension defect for auditory or visual material. No abstraction defect: normal performance on Weigl's sorting test.

There were gross defects in the *visual-constructional* sphere: The patient could copy only the first of Kohs' Block Designs and was unable to assemble the "Manikin" jig-saw in the Bellevue Object-Assembly Test. He had difficulty in copying the simplest geometrical designs and in drawing outlines of common objects from memory. He was able to describe the layout of his house accurately but unable to represent it coherently as a ground plan (fig. 2). There was pronounced neglect of the left half of visual space observed in reading or describing pictures. He was able to count small scattered objects but unable to work out the number of blocks comprised in a solid, regular cube. There was some visual disorientation in what remained of the left homonymous fields: he could apparently assess distance of remote objects fairly accurately in this part of the field but was unable to do so in the case of objects presented within his arm's reach. In representing the co-ordinates of space, he tended to tilt them in such a way that the horizontal

deviated upwards and to the left. There were no general psychiatric symptoms apart from a complaint of inability to concentrate. There were no gross personality changes. He had insight into the general nature of his disabilities but was unaware of their more intimate features.

Air-encephalography revealed a shift to the left of the anterior part of the left lateral ventricle, with angulation of the third ventricle and the septum. No air entered the right ventricle. The diagnosis was made of a right fronto-parietal tumour and a biopsy taken from this region established its nature as a glioblastoma multiforme. The patient received deep X-ray therapy but died at home five months after admission. No post-mortem examination was made.

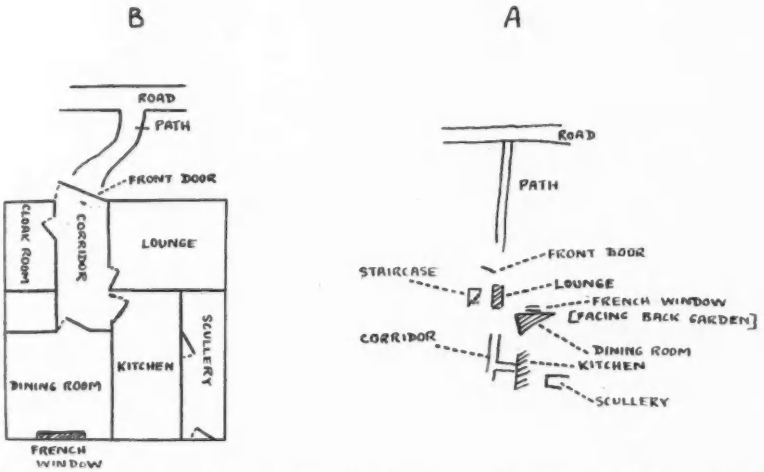

FIG. 2.—*Ground-plan of house by Case* 3. B. Plan by O. L. Z. A. Plan by patient.

The main points of interest in this case are (1) Neglect of left side of visual space, with some visual disorientation in the intact portion of the left half-fields; (2) gross visual-spatial defects, including distortion of the visual co-ordinates and associated constructional disabilities; and (3) gross defect of spatial representation but without loss of topographical memory. These disabilities were caused by a large tumour involving the fronto-parietal region of the right hemisphere.

Case 4.—A coal merchant, aged 46, was admitted with the complaint of severe frontal headaches and periods of "confusion" during which he would lose his way.

Six months previously, the patient began to notice difficulty in identifying coins and in mental arithmetic. This was followed by a number of episodes of losing his way: twice he missed his house on returning home and had great trouble in finding it. He would become lost while driving his lorry along familiar routes and on occasion actually lost himself in his own house, finding himself in the "wrong room." He also began to have difficulty in dressing—in putting on his clothes the wrong way round and confusing articles of dress. He noticed increasing memory loss, even to the extent of forgetting the names of his children.

Four months before admission, while driving his lorry, the road in front of him suddenly appeared to undulate and at the same time he saw a saw-tooth pattern.

This lasted about ten minutes. Following this, a severe right frontal headache developed and this recurred almost daily. Later, there were episodes in which his surrounding appeared distant or distorted and occasionally, when lying in bed, he felt that he was suspended in mid-air. In the two weeks prior to admission, he noticed *déjà vu* experiences with strangers.

On *neurological examination* fields were full to confrontation. Visual acuity 6/12 in both eyes. Gross papillœdema with hæmorrhage in right eye and early papillœdema in left. Slight ptosis of right eyelid. Cranial nerves otherwise normal. Increased tone and slight weakness in left arm and leg and difficulty in performing repetitive movements. Tendon reflexes brisk on both sides but exaggerated on left. Lower abdominals absent. Ankle clonus on left; both plantars flexor. Romberg's sign was absent. Sensation normal throughout except for slight impairment of position sense in left hallux. No apraxia.

On *psychological examination* pre-morbid intelligence was judged to be in high-normal range. Vocabulary (Wechsler-Bellevue): Score—31. Moderate impairment on psychometric tests of calculation and learning. No evidence of dysphasia. No comprehension defects or agnosia for objects or pictures. *Visual-constructive* performance was impaired, though not grossly so. The patient was able to copy simple designs, to complete unfinished capital letters and to count the number of blocks composing a cube. At the same time, he was unable to cut out a star-shaped figure, drawn on paper, with scissors (despite absence of apraxia) and he reproduced the disposition of a few objects exposed on a sheet of paper very poorly. There were also slight, though unequivocal, defects in drawing maps and ground-plans. No evidence of neglect of left half of space apart from his own admission that he thought most of the turnings which he missed when he became lost were on his left. No difficulty in counting scattered objects in the visual field. In representing the visual co-ordinates, he tilted the horizontal anticlockwise and the vertical clockwise. No right-left disorientation but on one occasion some degree of finger-agnosia was elicited.

Insight was good but there was some "catastrophic reaction" to intellectual testing. No outstanding personality change apart from slight increase in irritability.

After a biopsy in right parieto-occipital area, the patient's condition slowly deteriorated and he died three months after admission.

On *post-mortem examination* there were in the brain a number of secondary deposits from a bronchial carcinoma. The small ones, ranging in diameter from 6 to 25 mm., were (*a*) in the posterior part of the left middle frontal gyrus; (*b*) in the left supero-parietal lobule; and (*c*) in the right inferior parietal lobule. The large mass was on the right side, extending from the level of the massa intermedia backwards for 7 cm. to the superomedial white matter of the occipital lobe, partly filling the body of the right lateral ventricle, involving the choroid plexus, the centrum ovale, and invading the splenium of the corpus callosum. It measured 6 cm. in transverse diameter and 5 cm. vertically. The right optic radiation was not involved (fig.1c).

This case is of special interest in so far as there appeared to be marked episodic spatial disorientation and almost certainly some degree of topographical memory loss in the absence of outspoken defects in the visual constructional sphere. There was little, if any, agnosia for the left half of visual space. Although bilateral lesions were present in this case the major involvement was clearly on the right side.

Case 5.—An engineer, aged 36, was admitted complaining of "dreamy sensations" and later of weakness of the left limbs and visual disturbances.

Eighteen months previously, the patient began to have attacks in which his surroundings became strange and unreal, followed a few seconds later by a pungent smell like incense and a tingling sensation in the abdomen. These episodes lasted

about half a minute, without loss of consciousness, and occurred frequently during the next nine months, after which they ceased.

Nine months before admission, the patient began having frontal headaches and three months later his left leg suddenly became weak and difficult to control. The left hand next became weak and he found himself dropping articles from it because he did not " realize that they were there." At the same time, vision to the left deteriorated and he began bumping into things on this side. During this period he gained 2½ st. in weight and " always felt sleepy."

On *neurological examination* there was a left homonymous hemianopia, sparing the macula. The nasal margin of the right disc was blurred. Slight nystagmus on looking to right and upper and lower left facial weakness. The left arm and leg were slightly spastic, weak, and co-ordination and repetitive movements were impaired. There was left foot drop ; the left abdominal muscles were weak. Tendon reflexes exaggerated on the left ; abdominals absent on left ; left plantar response extensor. The left leg dropped in walking, and, on standing heel-to-toe, he fell to left. Pain, temperature and touch were normally perceived throughout. Vibration and joint position sense were normal. Impairment of two-point discrimination on left arm and leg and astereognosis in left hand.

On *psychological examination* pre-morbid intelligence was placed in the superior range. Vocabulary (Wechsler-Bellevue) : Score—38. No psychometric evidence of general deterioration. No evidence of comprehension defect or dysphasia. Occasional neglect of left half of pictures on special tests.

Visual-spatial performance markedly impaired. Patient was able to copy very simple designs but unable to draw a cube, or cut a star out of a piece of paper. Block designs were impaired but not grossly. Ground-plans were accurate apart from some confusion in representing doors. Map drawing was grossly disorganized (cf. fig. 5). There was marked neglect of left side of visual space and gross errors in counting an irregular assembly of small scattered objects in the visual field. There was no disorientation for right and left. No evidence of personality change.

Following arteriography and ventriculography, a biopsy was taken from right temporal region, but the patient died the following day, two weeks after admission.

On *post-mortem examination* there was a glioma in the right temporal lobe, lying medially and inferior to the lateral ventricle, and extending from the level of the rostrum of the corpus callosum anteriorly to the level of the posterior part of the body of the lateral ventricle (fig. 1D).

The main psychological features in this case are (1) Neglect of the left side of visual space ; (2) gross visual-constructive defects ; and (3) defects in topographical representation but without established defect of topographical memory.

Case 6.—A schoolmistress, aged 55, was admitted complaining of headache and visual disturbances.

For seven years there had been a slowly progressive failure of vision, more apparent in the right eye. Recently, reading had become difficult. There was a history of occasional episodes of unsteadiness on her feet (not true vertigo) and occasions on which a feeling of " pins and needles " spread up left side from the foot. A year before admission she had severe occipital headaches, with vomiting, lasting two weeks. For two to three months, she had intermittent burning pains in right face. Also a little urgency of micturition.

On *neurological examination*, V.A.R. 6/18 ; V.A.L. 6/9. Bilateral lower nasal quadrantic restriction of fields. Opacities in both lenses, more marked on right. Moderate bilateral papillœdema. Right pupil was smaller than left. In the distribution of the trigeminal nerve, there was motor paralysis with hypalgesia and hypæsthesia in all divisions. Corneal reflexes absent on right. Gait unsteady and Romberg's sign positive. Tone and power in arms and legs equal on both sides and

no impairment of co-ordination or repetitive movements. Tendon reflexes brisk bilaterally. Plantar responses both flexor. Pain and temperature sensation normal. Touch, vibration and joint-position sense impaired over lower parts of both legs.

On *psychological examination* pre-morbid intelligence was placed in high-normal range. Vocabulary (Wechsler-Bellevue): Score—30. Psychometric evidence of mild non-specific deterioration. No dysphasia, comprehension defect or visual agnosia for objects or pictures. No evidence of abstraction defect: normal performance on Weigl's sorting test.

There were pronounced defects in visual-constructive sphere. Progressive matrices (Raven, 1938): Score—18/60. Block Designs (Wechsler-Bellevue): Score—9. She was able to copy only the simplest geometrical designs and drawing from memory was very poor. She was unable to count scattered objects or to perform the cube-analysis test (Paterson and Zangwill, 1944). Insight was poor, with some tendency to "catastrophic reaction."

Air-encephalography showed evidence of a right hemisphere expanding lesion, confirmed by ventriculography. Six months after admission a right parasagittal meningioma was removed at operation.

This patient is of interest on account of the severe visual-spatial disabilities and the comparative lack of intellectual disturbances in other spheres. There was no agnosia for the left half of visual space and no history of topographical disorientation.

Case 7.—An upholsterer, aged 47, was admitted complaining of headaches and with a history of visual disturbances.

Five months previously the patient had had severe headaches daily over a period of a fortnight. Two months before admission these recurred and he visited his doctor. On the way, however, he became lost but managed eventually to recover his orientation. About the same time, his sight began to deteriorate and he was liable to knock into things on his left and to have difficulty in reading and dressing.

On *neurological examination* visual acuity (corrected) was 6/18 on the right and 6/36 on left. There was a bilateral incongruous left lower quadrantic hemianopia. Bilateral papillœdema with hæmorrhages and exudate. Also an old left facial palsy. Except for slight weakness in flexion of left hip, power normal in all limbs and no increase in tone. Tendon reflexes normal and plantar responses both flexor. Gait normal, but when standing with eyes shut patient tended to fall backwards and to left. Pain, temperature, touch and vibration senses normal. Slight impairment of joint-position sense in left hallux but two-point discrimination intact. No apraxia.

On *psychological examination* pre-morbid intelligence was found to be within average normal range. Vocabulary (Wechsler-Bellevue): Score—27. Moderate non-specific organic intellectual impairment on psychometric tests. No dysphasia. No agnosia for objects or pictures. No abstraction defect on Weigl's sorting test.

Visual-spatial performances were severely impaired even when care was taken to allow for the patient's poor visual acuity. He was able to copy only the simplest drawings and Block Design models, and quite unable to copy the outline of a cube. He was unable to execute the "paper-cutting" tests at the 9-year level of the Stanford-Binet scale (cf. Paterson and Zangwill, 1944), and unable to draw maps or ground plans or to solve simple verbal directional problems. There was some distortion of the visual co-ordinates: he represented the vertical as tilted clockwise and the horizontal anticlockwise. There was slight weakness of immediate visual memory. No right-left disorientation on himself but he was occasionally wrong when asked to designate examiner's left and right. He was unable to count a number of scattered objects in the visual field, even when he could see them distinctly. There was no evidence of personality change but insight into specific disabilities was very poor.

Arteriography demonstrated a meningioma about 8 cm. in diameter lying on the convexity of the parietal bone in its mid-portion, extending down to about 2 cm. above the tip of the auricle and medially to the supero-sagittal sinus. This was removed at operation four weeks after admission.

This patient exhibited gross defects in the visual-constructive sphere without appreciable agnosia for the left half of visual space. There was no evidence of a topographical memory defect but episodic apraxia for dressing was recorded in the history.

Case 8.—A shop-manageress, aged 52, was admitted complaining of failing vision, headaches and impairment of memory.

A year previously, the patient began to notice failing eyesight, " mostly in the left eye " and had had her glasses changed, but with little effect. Eight months before admission, she began to suffer from frontal headaches almost every morning, which passed off during the day. She also noticed that she was becoming lazy, irritable and forgetful. Her father confirmed these changes in disposition and added that she had latterly become very bad in finding her way about, often becoming lost in familiar surroundings. Two weeks before admission, headaches became worse and were associated with occasional vomiting.

On *neurological examination* visual acuity was 6/9 in both eyes. Left homonymous hemianopia, sparing the macula, and early bilateral papillœdema. Extinction on left to bilateral visual stimuli. Just detectable left facial weakness. No motor impairment. Tendon reflexes were all normal and plantar responses flexor. Pain, temperature and vibration sense normal. Minimal defect elicited in perception of touch, joint position sense and two-point discrimination in left arm and leg. Marked astereognosis in left hand. No aphasia, visual object-agnosia or apraxia, except on constructional tasks.

On *psychological examination* pre-morbid intelligence was placed in high-normal range. Vocabulary (Wechsler-Bellevue) : Score—29. Evidence of only slight non-specific impairment, mainly in rote verbal learning. No abstraction defect : normal performance on Weigl's sorting test.

Visual-spatial disabilities were severe. Only two block design tests could be copied in the prescribed time. The patient could copy only the simplest designs with pencil or matchsticks and was unable to draw or copy the outline of a cube, neatly to fold a sheet of paper and place it in an envelope, or cut out a star from paper. Drawings from memory of common objects, maps or ground-plans were grossly disorganized. There was *gross neglect of left half of visual space*, with extinction. Patient often bumped into objects on the left and failed to notice left-hand side of pictures or a page of print. Was inaccurate in counting scattered objects in the visual field and in cube-analysis (Paterson and Zangwill, 1944). Right-left orientation correct on herself but often wrong on examiner or with relation to external objects. Deformation of the visual co-ordinates, with horizontal tilted anticlockwise and vertical clockwise.

There was some increase in irritability during her illness and co-operation at times was uncertain during the mental examination. She showed a profound lack of insight into her visual-spatial disabilities, so marked as to suggest an anosognosic reaction.

Arteriography showed evidence of expanding lesion in temporo-parietal region on right side. Right parietal parasagittal meningioma removed at operation six weeks after admission.

The main features of psychological importance shown by this patient are : (1) Unilateral agnosia for the left side of visual space ; (2) gross visual-spatial defects on special tests including deformation of the visual co-ordinates ; (3) constructional apraxia ; (4) impairment of

oculomotor co-ordination and control in reading and counting scattered objects in the visual field ; (5) history of disturbances in the topographical sphere ; and (6) lack of insight into visual disabilities.

III. Distribution of Visual-Spatial Defects

We may now consider briefly the principal symptoms of psychological interest shown by the above series of patients and examine their distribution in the series as a whole.

(1) *Visual field defects :* A left homonymous hemianopia was present in 6 cases, with macular sparing in all but one. The defect was incomplete in one patient (Case 3), who showed a visual disorientation (Riddoch, 1935) in what remained intact of his left half fields. In Case 6, there was a lower binasal quadrantic defect. Extinction to bilateral visual stimuli on the left side was noted in Case 8.

(2) *Unilateral spatial agnosia :* Neglect of the left half of visual space was present in greater or less degree in 6 cases. It was most pronounced in Cases 1, 2 and 8; moderately pronounced in Cases 3 and 5, and barely appreciable in Case 4. In no patient was this agnosia associated with any marked tendency to neglect the left half of the patient's own body.

(3) *Oculomotor defects :* No disturbance of fixation comparable to that described by Paterson and Zangwill (1944, Case 2) was observed in the present series. On the other hand, 5 patients were notably impaired on tasks involving the counting of an irregularly disposed assembly of objects in the visual field (even when allowance was made for unilateral spatial agnosia) and 6 reported difficulties in following the lines in reading (cf. Holmes, 1919, 1938 ; Paterson and Zangwill, 1944). In 2 patients (Cases 3 and 4), no defects of this nature could be elicited.

(4) *Apraxia for dressing :* Difficulties in dressing were reported by 4 patients. They were outspoken in Cases 1, 2 and 7 and altogether slighter in Case 4. These difficulties appeared to be due to confusions regarding top and bottom, back and front, and right and left with reference to the garments. In Case 4, it was specifically reported that the patient was unable to tie his tie, as in the case reported by Marie *et al.* (1922). In no case was there evidence of motor, ideomotor or ideational apraxia as ordinarily defined.

(5) *Deformation of visual co-ordinates :* In 5 cases, rough tests were given in which the patient was required to represent the horizontal and vertical co-ordinates of space with eyes open and shut. No significant errors were made by Case 5. In Cases 4, 7 and 8, on the other hand, distortions were observed with eyes open agreeing closely with those described by Lenz (1944) in cases of right occipito-parietal injury. In one patient (Case 3), both the vertical and horizontal co-ordinates were displaced in a clockwise direction but without approximation of the axes.

(6) *Right-left disorientation :* No patient gave evidence of inability to appreciate left and right on his own body. In 3 patients, however, there was evidence of confusion of left and right with regard to the examiner's body or external objects (Cases 1, 7 and 8).

(7) *Visual-constructive disabilities :* Disorders in the appreciation of higher spatial relationships and in the execution of simple constructional tasks under visual control were outspoken in all 8 cases. These disorders were essentially of the type defined by Paterson and Zangwill (1944). They were extremely severe in Cases 1, 2, 3, 7 and 8 ; moderate in Cases 5 and 6 and comparatively mild in Case 4. A detailed analysis of the disabilities is given below.

(8) *Loss of topographical orientation:* 5 patients gave evidence from their history of a loss of topographical orientation in normally familiar surroundings (Cases 1, 2, 4, 7 and 8). This disorientation was as a rule episodic. In one patient (Case 4)

loss of topographical orientation could not be related to agnosia for the left half of space.

(9) *Loss of topographical memory :* A defect of topographical memory may be postulated in cases in which there is inability correctly to describe familiar routes and buildings despite absence of aphasia. As thus defined, topographical memory-loss was present in Cases 1 and 8 and suspected (although not definitely established) in Cases 4 and 6.

(10) *General intellectual impairment :* Psychometric studies indicated some degree of non-specific intellectual loss in 6 cases. This was graded as moderate in one (Case 4), mild in 5, and negligible or absent in 2 (Cases 3 and 5). In no case was there any pronounced defect in " abstraction " (in the sense of Goldstein) and only one patient (Case 2) failed on the Weigl Sorting Test, which demands some understanding of abstract principles. We may conclude, therefore, that there was relatively little general deterioration in this series of cases at the time at which the specific disabilities were made the object of our study.

The general distribution of the principal visual (and kindred) defects as classified above is shown in Table I.

TABLE I.—DISTRIBUTION OF VISUAL-SPATIAL DISABILITIES

	Cases							
	1	2	3	4	5	6	7	8
Visual field defects	+	+	+	−	+	+	+	+
Unilateral spatial agnosia ..	++	++	+	?	+	−	−	++
Oculomotor defects	+	+	−	−	+	+	+	+
Apraxia for dressing	++	++	−	−	−	−	++	−
Deformation of co-ordinates ..	NT	NT	−	+	−	NT	+	+
Right-left disorientation ..	+	−	−	−	−	−	+	+
Visual-constructive disabilities	++	++	++	+	+	+	++	++
Topographical disorientation ..	+	+	−	+	−	−	+	+
Loss of topographical memory	++	−	−	+?	−	+?	−	++
General intellectual impairment	+	+	−	++	−	+	+	+

++ severe impairment ; + moderate or mild impairment ; − no demonstrable impairment ; NT not tested.

IV. ANALYSIS OF VISUAL-SPATIAL DISABILITIES

Spatial-agnosic defects, as Marie *et al.* (1922) pointed out, bear essentially on spatial representation and its relation to the performance of voluntary movements. Although form, pattern and colour are normally perceived and distance judgment (in central vision at least) shows little or no impairment, the patients consistently fail on tasks which demand fine spatial discrimination or the explicit analysis of spatial structure. One may say, with Lhermitte (1933), that there is a circumscribed dissolution of *la pensée spatiale*.

These visual-spatial defects were well brought out on the following special tests :

The Cube-analysis Test (Paterson and Zangwill, 1944) requires the patient to compute the number of one-inch cubes (usually 27) contained in a solid and regular cube placed before him. This test gave great difficulty to all the patients in this series. Although some of the errors made were undoubtedly due to neglect of the left side of the cube, the fact that over-estimations were as common as under-estimations demonstrates that this cannot be the sole source of error. Again, although difficulties in the oculomotor sphere may have contributed to the difficulty, it was noteworthy that there was no regular correspondence between patients who

failed in cube-analysis and those who experienced the greatest difficulty in counting an assembly of small items (e.g. pins) scattered at random in the central field of vision. Thus, Case 3, who had no difficulty in visual counting, failed signally on the cube-analysis test. It may be surmised, therefore, that proper performance of this task demands an awareness of spatial articulation which is not demanded on tests of counting disjoined objects. Further, the low scores obtained on the Progressive Matrices test by Cases 1, 2, 3 and 6 provides further evidence for the existence of a primary high-level agnosic disability.

Disturbances on tasks which demand a motor or constructional response properly co-ordinated with the spatial properties of the visual field are often represented as *constructional apraxia*. It appears virtually certain, however, that they rest largely, if not exclusively, upon a spatial-agnosic basis (Lhermitte and Ajuriaguerra, 1942 ; Paterson and Zangwill, 1944). All our patients manifested outspoken visual-constructive disabilities :

Copying and Drawing : Copying of simple designs, with pencil or matchsticks, was very poor in all patients. Performance on drawing tests was marked by (*a*) faulty articulation of component parts, especially with regard to angles other than right angles ; (*b*) failure to join up component lines ; and (*c*) faulty orientation of the pattern as a whole with reference to the background provided by the paper. It was noted that disjunction of the parts of a complex pattern was more pronounced in the cases with severe grades of visual-constructive disability (Cases 1, 2, 3 and 8). In drawing common objects from memory, only two patients (Cases 4 and 5) showed comparatively little disturbance. In the remaining cases, performance was marked by (*a*) faulty orientation and articulation of parts of the object in relation to one another ; (*b*) confusion of planes (as described by Paterson and Zangwill, 1944 ; and Roth, 1949), and (*c*) simplification of outline. Thus it was notable that the patients could represent the individual parts of a complex object, such as a chair or bicycle, in a recognizable fashion but appeared unable to relate or assemble these components to form a coherent whole (cf. fig. 3).

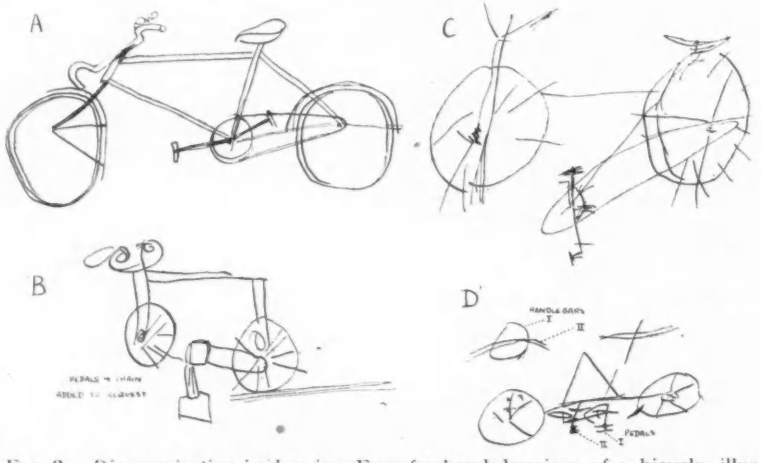

FIG. 3.—*Disorganization in drawing.* Four freehand drawings of a bicycle, illustrating varying degrees of visual-spatial disorganisation. A. Case 5. B. Case 1. C. Case 7. D. Case 3.

These findings suggest that errors in copying and drawing arise from a peculiar inability to maintain a consistent viewpoint or frame of reference. The most striking features are errors of articulation and confusion of planes. There is no suggestion of a primary executive disability, in the strict sense of constructional apraxia.

Assembly and construction : Analysis of performance on block design tests of the Kohs type reveals the following features : (*a*) Failure to arrange the four presented blocks to form a square (observed in several disturbed cases) ; (*b*) inability to appreciate the number of blocks required to copy a given design (defect of spatial judgment) ; (*c*) defective orientation of the internal pattern or figure in relation to the square framework or background. Only Case 2 failed to build a square from four blocks under all conditions but three patients (Cases 1, 3 and 8) were unable to do so when the required pattern was at all complex. Errors of orientation of the " figure " in relation to the " ground " were prominent in all cases but there was marked individual variation in the level of complexity of task at which such errors occurred. Thus Cases 1 and 2 showed grave errors on the simplest designs, appreciating little more than the difference in colour of " figure " and " ground." In Cases 4 and 5, gross structural features of the " figure " were adequately reproduced but not accurately fitted to the background. It is also noteworthy that several patients, when comparing their copies with the corresponding models, failed to appreciate even gross errors in their reproductions.

Comparable defects were in evidence on many other simple assembly tests. Thus Case 2 was quite unable to assemble a " Manikin " figure when given pieces representing the head, limbs and trunk. She placed the trunk upside down and attempted to fit in both the arms and legs at the level of the waist. The head was placed at a peculiar angle to the trunk and the resulting asymmetry not appreciated (fig. 4).

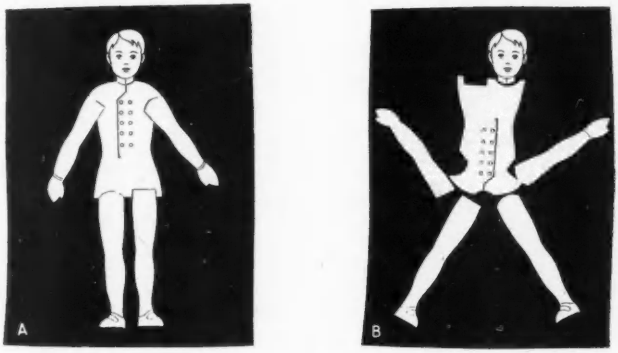

FIG. 4.—*Assembly of " Manikin " Figure by Case* 2. A. Correct Assembly. B. Assembly by Patient.

One may add that correct execution of this assembly test is usually well within the capacity of the average 8-year-old child.

Characteristic errors were also observed on simple tests in which the patient was merely required to copy or reproduce the spatial arrangement of a small number of discrete objects.

Form-arrangement Test : Three cardboard figures, a disc, a square and a triangle were arranged at random on a large sheet of paper and the patient required to

reproduce the arrangement with similar pieces on a piece of paper of the same size. 3 of the 4 patients to whom this task was given made rather gross errors in their disposition of the figures, in relation both to one another and to the background. It was of interest to note that Case 4, who showed relatively little impairment on drawing and assembly tests, made clear-cut errors on the present task. This might suggest that reproducing the spatial relationship of disjoined objects affords especial difficulty, perhaps in view of the more precise perception of the spatial properties of the situation which it entails.

Defects comparable to those brought out on the various special tests were also elicited on a number of activities of a less artificial and more everyday character. Apart from dressing (which is considered below), it was thought of some interest to see whether the patients could carry out a sequence of habitual activities such as folding a letter, inserting it in an envelope, addressing it and affixing the stamp. It was found that all the patients could perform the required acts in proper sequence and without executive errors of an apraxic nature. But there appeared to be gross impairment of spatial judgment. Thus the sheets of paper were commonly folded in an uneven and untidy manner and the flap of the envelope folded over in an unsymmetrical way. The lines of the address were poorly oriented on the envelope and in some cases the stamp was affixed upside down or at an unusual angle. Sometimes one stamp was affixed in such a manner as partially to cover another. These errors were not due to carelessness ; indeed the patients took particular trouble to perform the required task as carefully as they could and appeared to have little or no appreciation of the unsatisfactory nature of the result.

Apraxia for dressing was ascertained in 4 patients (Cases 1, 2, 4 and 7). This disability arises in various ways and the responsible causal factors differ from case to case (Russell Brain, 1941 ; Hécaen and Ajuriaguerra, 1942–45). In the present cases, it would appear that the principal conditions of the dressing disability were (*a*) neglect of the left half of the garment (Cases 1 and 2) ; and (*b*) impairment of visual-spatial judgment (present in all cases). The second factor showed itself in the difficulty experienced by the patients in distinguishing between the left and right (and occasionally the top and bottom) of the garment. A neat illustration of the origin of the disability in the visual-spatial sphere is provided by Case 4, who could tie his tie *except* when regarding himself in a mirror.

Disorders in the *topographical sphere* were noted in 5 cases (1, 2, 4, 7 and 8). In no case, unfortunately, could observations be made of the behaviour of the patients in their home surroundings, as in the case reported by Paterson and Zangwill (1945). In the light of the case histories, however, there appears to be no doubt that episodes marked by loss of topographical orientation had taken place while the patients were in surroundings normally well known to them. In 4 of these cases, the tendency to ignore the left side of visual space may well have contributed to the disability. In one of these cases, however, the patient was observed while in hospital to miss turns to the right as well as to

the left, suggesting that further factors are almost certainly involved. It is also noteworthy that not every patient with evidence of unilateral spatial agnosia experiences difficulty in spatial orientation. One may conclude, therefore, that a more complex disorder of place-recognition is responsible for the disability.

The representation of topographical relationships by simple maps or ground-plans was impaired in all 8 cases.

Map drawing : All patients drew extremely poor maps of the British Isles—so poor as to suggest a specific disability. Several, too, experienced difficulty in demonstrating the location of important towns on a map provided. In many cases, disorders in map drawing appeared to derive from what Paterson and Zangwill (1944) termed the *piece-meal approach* and the implied difficulty in maintaining a consistent spatial framework. Case 1, for instance, drew a recognizable map of the British Isles and placed London and Newcastle in roughly correct positions. When asked to denote Edinburgh and Glasgow, however, he placed both cities well to the south of Newcastle. It transpired that the patient was now treating the central area of the map *as if* it represented a map of Scotland. Case 5 provided us with an even more striking illustration of local disorientation on the paper (fig. 5). This

FIG. 5.—*Drawing of map of England by Case* 5. This drawing illustrates progressive disorientation on the paper.

patient, when attempting to outline the coast-line of Britain, drew first the west coast and, having reached Land's End, turned the paper through a right angle and continued with the south coast, drawing it approximately parallel to the west coast. He was quite unable to appreciate the nature of the disorientation which had insinuated itself into his drawing.

Ground-plans : Ability to draw a ground-plan of the patient's own house was tolerably well retained by Cases 4 and 5 but grossly impaired in the remaining cases. Of particular interest is the fact that one of these patients (Case 3) had been living for the past fifteen years in a house which had once been occupied by one of the present writers (O. L. Z.). A ground-plan of this house drawn by the patient (fig. 2A) may be compared with one drawn by ourselves from memory (fig. 2B). It will be seen that the patient not only failed to block out his plan but proceeds in a " piece-meal " fashion and makes several mistakes in the relationship of the various rooms. On the other hand, this patient's verbal accounts of the lay-out of the house and of the general topography of the neighbourhood were esentially correct. In this case, then, there was gross representational disability with intact verbal-topographical memory.

A dissociation between errors of topographical representation and accurate topographical description, such as we have described in Case 3, was by no means invariable. Case 8, for instance, made many serious mistakes in her descriptions of routes, buildings and squares in parts of London hitherto well known to her. In this case, too, it is probable that the difficulties in route-finding prior to her admission to hospital derived from a topographical agnosia comparable to that described by Paterson and Zangwill (1945) in a case of brain injury involving the posterior part of the right temporal lobe. As we had no opportunity of examining this patient's behaviour outside the hospital, however, such an interpretation must remain purely speculative.

V. Discussion

The present series of cases is of interest in displaying a consistent pattern of visual-spatial disability correlated with a lesion involving the posterior portions of the right cerebral hemisphere in right-handed individuals. This disability has been variously described as apractognosia for spatial articulation (Lange, 1936), planotopokinesia (Marie *et al.*, 1922), or, more simply, as visual-constructive derangement (Paterson and Zangwill, 1944). It is marked by gross inability to apprehend or reproduce all but the simplest visual-spatial relationships and by a peculiar restriction and fragmentation of visual perception in its spatial aspects. In 6 cases, this defect was found to be associated with the syndrome of neglect of the left side of visual space (unilateral spatial agnosia) which is known to arise from parietal involvement of the minor hemisphere (Russell Brain, 1941, 1945). Arising, in part at least, from these two major defects are a number of more specific visual-spatial disabilities. These comprise difficulties in right-left orientation with regard to external objects, errors in route-finding, apraxia for dressing and constructional anomalies. In addition, high-grade disturbances of oculomotor co-ordination and control were found to be present in 5 of our cases. The

pattern of disability is remarkably clear cut and is associated neither with significant impairment of general intelligence nor with language disorder. Personality changes are minimal.

The question of whether the oculomotor anomalies observed in certain of our cases are primary or secondary to the perceptual disturbance has been debated at some length in the recent literature (Holmes, 1938; Paterson and Zangwill, 1944; Hécaen and Ajuriaguerra, 1949). The present observations have nothing new to contribute towards the solution of this problem which, as Hécaen and Ajuriaguerra (1949, p. 300) point out, is at present a matter for discussion rather than clinical study. We hope, however, to report in the near future an analysis of eye-movement records in cases such as those reported in this paper which may throw some light on the problem. It is clear from the present study, however, that gross perceptual disabilities may be present in cases without appreciable defect in the oculomotor sphere.

It is pertinent to inquire whether the slight differences in symptomatology from case to case may be correlated with any clear-cut differences in the localization of the responsible lesions. Unfortunately, examination of the neuropathological findings (in cases in which they are available) does not permit any simple answer to be given to this question. We are unable, for instance, to specify any consistent feature which might account for the presence of topographical memory loss in some cases though not in others. Hécaen and Ajuriaguerra (1949) have claimed that topographical memory is most commonly represented in the dominant hemisphere. But the presence of gross topographical memory loss in at least 2 of our cases, with unequivocally unilateral minor hemisphere lesions, is difficult to reconcile with this hypothesis.

It is of interest to note that 4 of the 5 cases in which episodes of topographical disorientation had taken place displayed extremely severe disturbances in the visual-constructive sphere. Apart from the factor of unilateral spatial agnosia, which in and by itself can provoke grave errors in route-finding, it might be argued that defects in place-recognition represent merely an extreme manifestation of visual-spatial agnosia and do not constitute a separate syndrome. At the same time the fact that episodes of topographical disorientation may occur without gross impairment of visual judgment or unilateral spatial agnosia (as in Case 4) is not easy to reconcile with this argument. On the evidence of this case and of many others of the same kind reported in the literature (cf. Hécaen and Ajuriaguerra, 1949, p. 302), it may be that, in the absence of unilateral spatial agnosia, some degree of *bilateral* cerebral involvement is an essential condition for topographical disorientation. As in so many problems of this kind, final answers must await the outcome of more systematic clinical study.

In conclusion, we may inquire whether visual-constructive disabilities of the type described in this paper are correlated in any specific fashion with lesions of the minor hemisphere or whether, as is generally held,

they may be elicited in cases with unilateral occipito-parietal lesions of either hemisphere. Impaired performance on visual-constructive tasks is extremely common in cases with occipital, occipito-parietal, or parieto-temporal lesions of the left cerebral hemisphere ; indeed the most striking instances of constructional apraxia have been reported in case of left-sided cerebral involvement. As we have pointed out in the Introduction, however, there is a steadily increasing body of evidence suggesting some more specific association between visual-spatial organization and the activity of the minor hemisphere. Apart from earlier clinical studies of visual-spatial agnosia associated with right-sided cerebral lesions in right-handed individuals (e.g. those of Scheller and Seidemann, 1932, and Dide, 1938), there are the more recent experimental observations of Lenz (1944), Paterson and Zangwill (1944), Bender and Jung (1948), and others, which suggest that the right occipito-parietal area may conceivably subserve some special function relating to visual-spatial cognition. Our personal observations (not yet published) are also leading us to the view that the pattern of visual-spatial and constructional disability commonly found in cases with left-sided cerebral involvement differs in subtle respects from the typical pattern described in the present series of cases with predominantly right-sided cerebral lesions. This might suggest that there is a certain " division of labour " between the two hemispheres in regard to visual-spatial organization. Until these observations have been fully worked out and confirmed, however, we cannot claim any exclusive role for the minor hemisphere in visual-spatial organization, as has been postulated by Lange (1936), Dide (1938) and Lenz (1944). It is felt that any such conclusion should be based not on an assembly of selected cases but upon the outcome of controlled clinical and experimental observation. For the present, we wish merely to place our existing observations on record and to comment on the consistency of the clinical picture in the series as a whole.

VI. Summary

(1) Recent studies of visual-spatial disabilities observed in cases with unilateral cerebral lesions are reviewed and evaluated. The comparative frequency with which such disorders have been reported in cases of right-sided occipito-parietal lesions is stressed.

(2) 8 cases are reported in which gross disturbances were established in the perception of spatial relationships and in the execution of constructional tasks under visual control. The lesion was exclusively or predominantly right-sided in all cases and the post-mortem findings are presented in 4. The evidence in these cases suggests that the right occipito-parietal region of the cortex was predominantly involved.

(3) The distribution of the principal visual-spatial disabilities in this series of cases is analysed and their relative severity assessed.

(4) Psychological investigations of the visual-constructive impairment are described. On the evidence of these findings, it is suggested that

apraxia for dressing and the greater part of the constructional disability can be exp'ained in terms of neglect of the left side of visual space (unilateral spatial agnosia) and a disorganization of discriminative spatial judgment (planotopokinesia).

(5) The origin and nature of the topographical disturbances observed in certain of the patients are considered. It is pointed out that unilateral spatial agnosia is not the sole cause of this disability.

(6) The relation of visual-constructive disturbances to lesions of the major and minor hemispheres respectively is discussed. It is pointed out that although the evidence is not inconsistent with the view that the minor hemisphere is of some special significance in regard to visual space perception, a decisive conclusion on this point must await the outcome of more extensive clinical study.

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CORTICAL RHYTHMS NOT SEEN IN THE ELECTRO-ENCEPHALOGRAM

BY

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AFTER spontaneous electrical rhythms had been recorded from the scalp by Berger (1929) similar records had to be made from the surface of the brain to decide whether the scalp records (electroencephalograms) were a true reflection of the pial records (electrocorticograms). As a result of experimental investigation it became recognized and generally accepted that the two records were similar, and that the differences in them were simply due to the different physical properties of the recording methods (Foerster and Altenburger, 1935; Walter, 1937; Schwartz and Kerr, 1940). Records taken from the nasopharynx, too, have been shown to be indistinguishable in quality from those taken with the routine scalp leads (MacLean, 1949). The distance of the scalp electrodes from the source of origin of the rhythms, the electrical resistance of the tissues, and to a lesser extent the electrical activity arising in the tissues themselves change the records a little. There is a lowering of the voltage, loss of detail, and some distortion of wave form caused by the superimposition of the potential differences arising at each of the two electrodes. In the main, however, the records from scalp and cortex are similar with similar technical methods, with special regard to the electrode placing and amplifier characteristics.

The records made through "bipolar" and "monopolar" electrodes differ, and the protagonists of each of these alternative techniques have kept up a brisk defence of their merits, although each is only a compromise. This compromise has arisen because of the physical and physiological properties of the cranium, which make the use of a true indifferent reference electrode impossible. Because of this the electroencephalogram, whether recorded from two points on the scalp ("bipolar") or from one point on the scalp and a diffuse area of the base of the skull conducted through the pinna ("monopolar") cannot truly indicate what is happening at one point in the cortex. This matter has been discussed by many reviewers, including Jasper (1942). Because of this difficulty also, the two methods of recording are considered complementary (Williams, 1938).

With these reservations it has been generally accepted that the electro-encephalogram reflects the more evident electrical activity of the underlying cortex, but it has come to our notice that in certain circumstances this is not so. This paper records some of the evidence.

Method

The observations were made when recording in the usual way from surface electrodes and simultaneously from a series of point electrodes at different depths in the cerebral substance. The method has been fully described (Williams and Parsons-Smith, 1949). These records, in which the plane of recording of the potential differences in the cortex is at right angles to the scalp, have been compared with other records in which the plane is parallel to the scalp.

Results

(1) *Comparing the E.E.G. with similar records from the dura mater.*—The observations of the earlier workers were confirmed by obtaining records from electrodes lying on the surface of the brain and comparing them with records obtained under similar circumstances from the overlying scalp with "unipolar" and "bipolar" methods of recording. Examples of "unipolar" records are shown in fig. 1. The records are

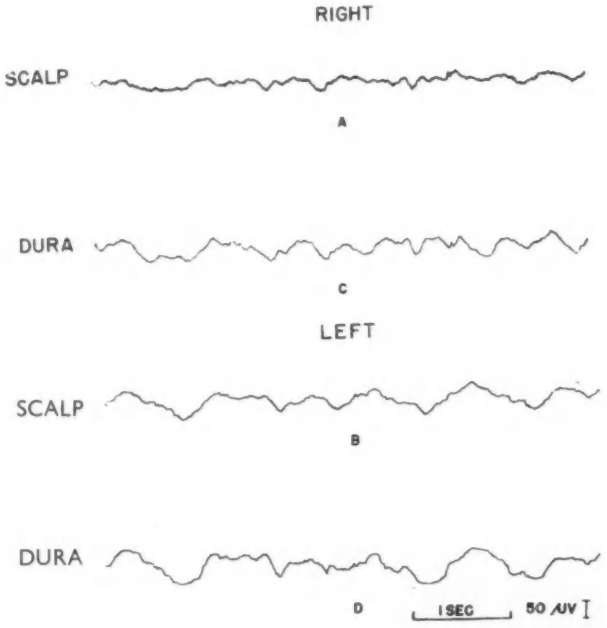


Fig. 1.—Simultaneous monopolar records obtained with the same amplification from both hemispheres through electrodes placed on the scalp (A and B) and on the underlying dura mater (C and D) in a patient with a malignant glioma of the posterior part of the left hemisphere. The dural records are similar to the E.E.G. but have a higher voltage and greater definition of wave form.

very similar, those obtained directly from the brain (C and D) having a higher voltage, a clearer definition of wave form and freedom from potential changes arising in surface tissues (A and B). *It is clear that E.E.G. records made from electrodes placed on the scalp usually have the same general features as those made from similar positions on the meninges.*

(2) *Comparing the E.E.G. with records made through the depth of the cortex.*—Examples of several records of this sort are shown in the paper which has already been quoted (Williams and Parsons-Smith, 1949), in which the method used is also described. The illustrations in that paper show clearly that *records made from two points on the scalp may be similar to those made from two punctate electrodes recording across the depth of the cerebral cortex.*

Two cases follow in which this was not the case.

Case 1.—A man aged 28 had had epileptic attacks for fifteen years with increasing motor disability which has made him bedridden for four years. There was no family history of epilepsy. He had one or two major convulsions a month and frequent falling attacks without loss of consciousness which were induced by sudden stretching of leg muscles. For seven years his limbs have jerked when they have been stretched and as this disability has increased he has become progressively more helpless. Mentally he seemed to be normal.

On examination frequent jerking and spasmodic movements of the whole body occurred spontaneously and in response to almost any form of stimulation. They were induced particularly easily by stretching a muscle. There was nystagmus, gross dysarthria and a spastic tetraplegia with contractures. Ventriculography showed symmetrical dilatation of the ventricles with excess of subarachnoid air. The appearances indicated marked cortical atrophy. Other routine investigations were negative. The electroencephalogram (25.4.49, Dr. W. A. Cobb) showed little occipital activity. In all areas there were very low voltage irregular waves of 4 to 7 a second. It was considered an abnormal record without any definite epileptic wave forms. Samples are shown in fig. 2 A and B.

Records were obtained with an insulated brain needle carrying four chlorided point electrodes to which the needle acted as an earthed shield. The electrodes were at the tip, and 2, 4, and 6 cm. from it. Records were made with the most superficial electrode 4 cm., 3 cm., 2 cm., and 1 cm. below the surface of the scalp. At the same time records were made of the potential differences between the more superficial of the needle electrodes and each of two silver cup electrodes sealed to the scalp in the frontal and parieto-occipital regions. Electroencephalograms were recorded from these electrodes and at different times in an antero-posterior direction on each side, and transversely. The figures make it clear that steps were taken to exclude amplifier differences, and surface records were made from different points of the scalp by "unipolar" and "bipolar" techniques, the electrodes within the hemispheres being in varying relationship to the cortex. The plane of the line of intracerebral electrodes was always at right angles to the scalp.

Routine E.E.G.s had also been recorded on other days. The surface E.E.G.s which invariably showed flat and rather featureless records (fig. 2A, and B) were disturbed from time to time by epileptic discharges and the movement artefacts of attacks which are not relevant to these observations. We were surprised to find in such a severe case of epilepsy so featureless a series of E.E.G. records. The needle electrogram showed a

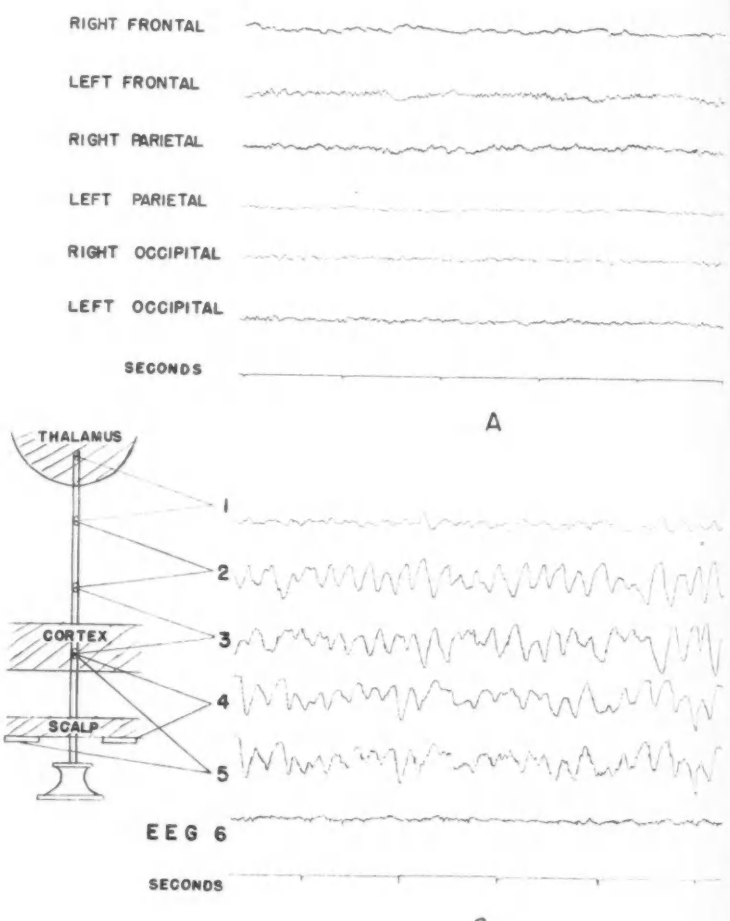
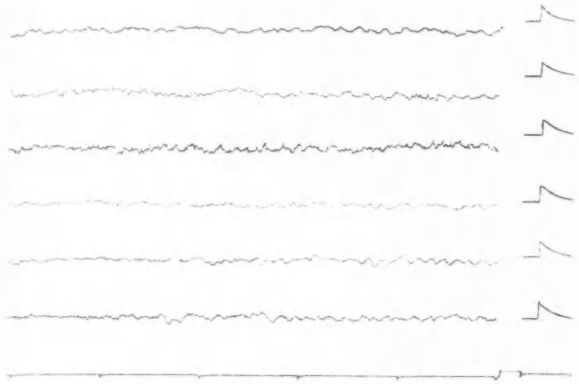
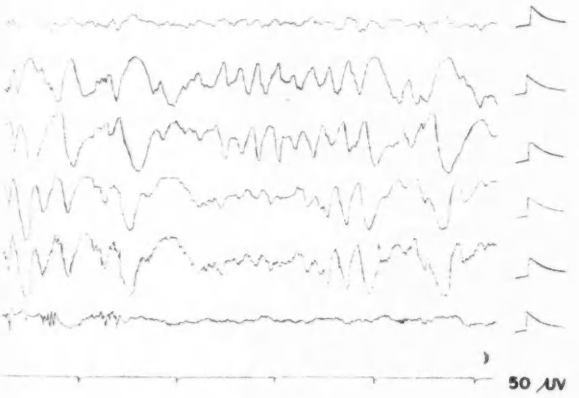


FIG. 2 (*Case* 1).—A: E.E.G. No dominant frequency can be recognized in the occipital leads. A low voltage 4–5 a second rhythm can just be discerned in the parietal leads, but the records are relatively flat. B: E.E.G. A rhythm of 8 a second is just evident in the occipital leads, and a low voltage rhythm of 4 a second can be seen to occur periodically in the frontal and parietal areas. The records were made on the same day as C and D but a week after A. C: The E.E.G. (lead 6) was recorded with the same amplification and amplifier characteristics as those used for the needle electrographic records. The only difference was that whereas the resistance through the scalp electrodes was 3,000 ohms, it was 100,000 ohms through



B



D

the minute electrodes within the cerebrum. These needle electrographic records show that there is a rhythm of 4 to 5 a second waves arising in the cortex (*see* phase reversal between leads 2 and 3) and not being propagated to the thalamus. These rhythms cannot be seen in the E.E.G. but they can be recorded when the cortical electrode is coupled with either scalp electrode. D: In D similar physical conditions exist, but high voltage episodic waves are occurring. They are represented in the records in the same manner as the rhythmic waves in C, and on this occasion are related with a burst of fast activity to be seen in the E.E.G.

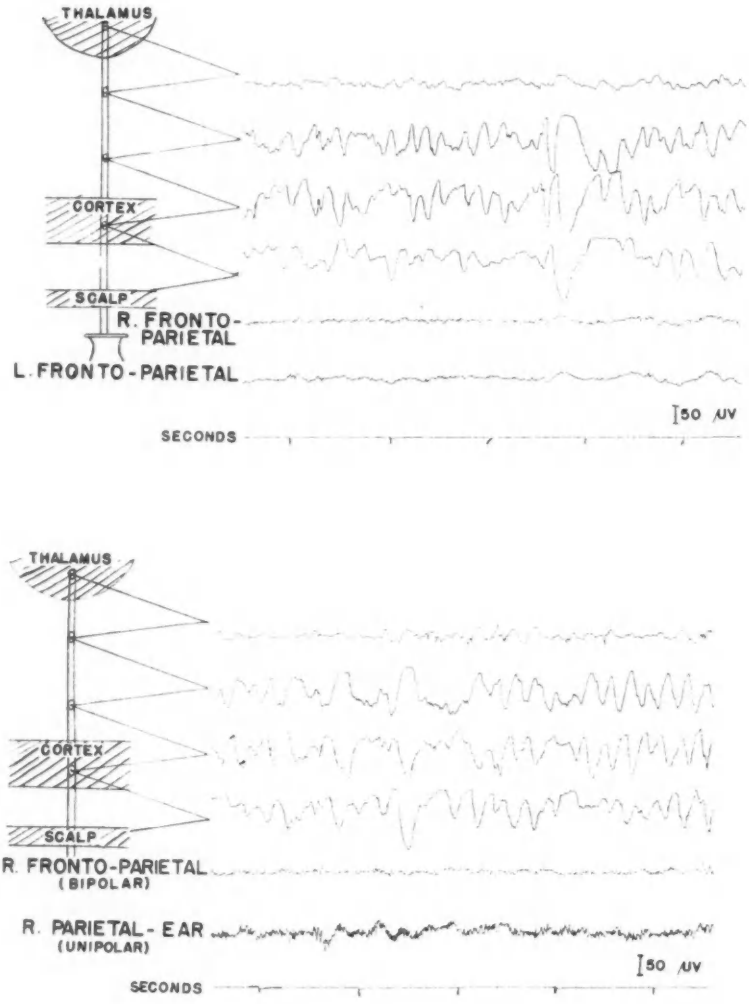


FIG. 3 (*Case* 1).—Records which show that the high voltage rhythmic changes recorded with the needle electrodes are not evident in the electroencephalogram recorded from the overlying scalp by " unipolar " as well as by the " bipolar " technique. The recording is otherwise similar to that in fig. 2. Notice the phase reversals occurring in the neighbourhood of the cerebral cortex.

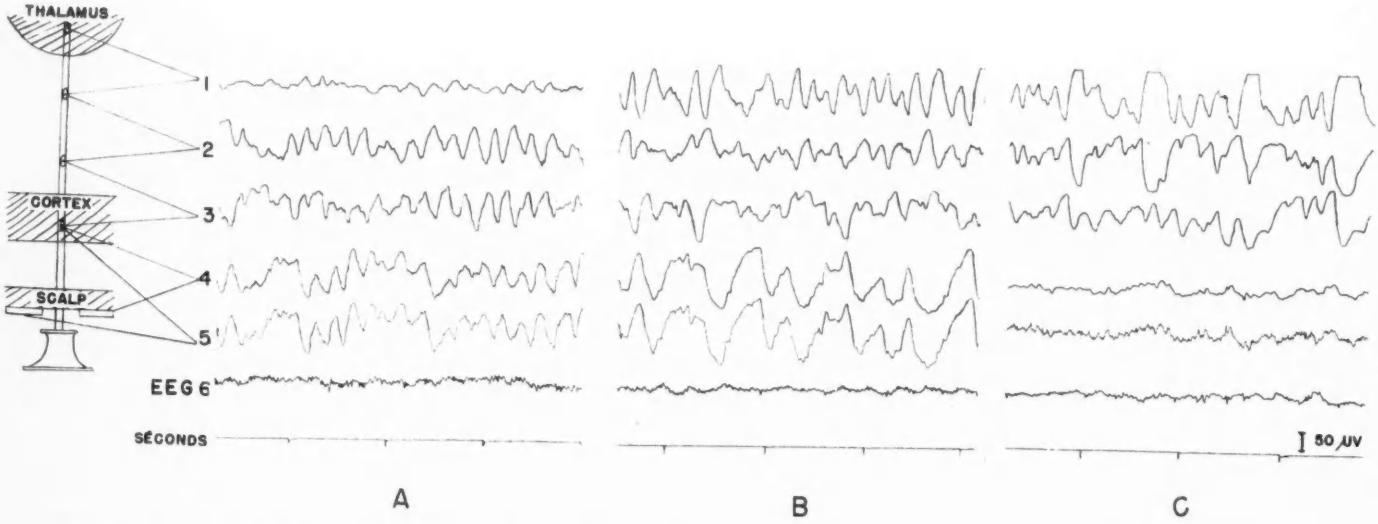


FIG. 4 (*Case* 1).—In A the electrode positions and recordings are as in fig. 2C. In B the needle electrodes have been withdrawn 1 cm. The intracerebral records have consequently moved up and the rhythmic 4 a second waves previously seen in lead 2 now occur in lead 1. The character of the record happens to have changed, but the relationship of the needle electrographic records to the E.E.G. remains unchanged. In C the needle electrodes have been withdrawn a further 2 cm. The two superficial electrodes are now in the scalp and superficial to the cortex respectively. The records have become identical with the E.E.G.

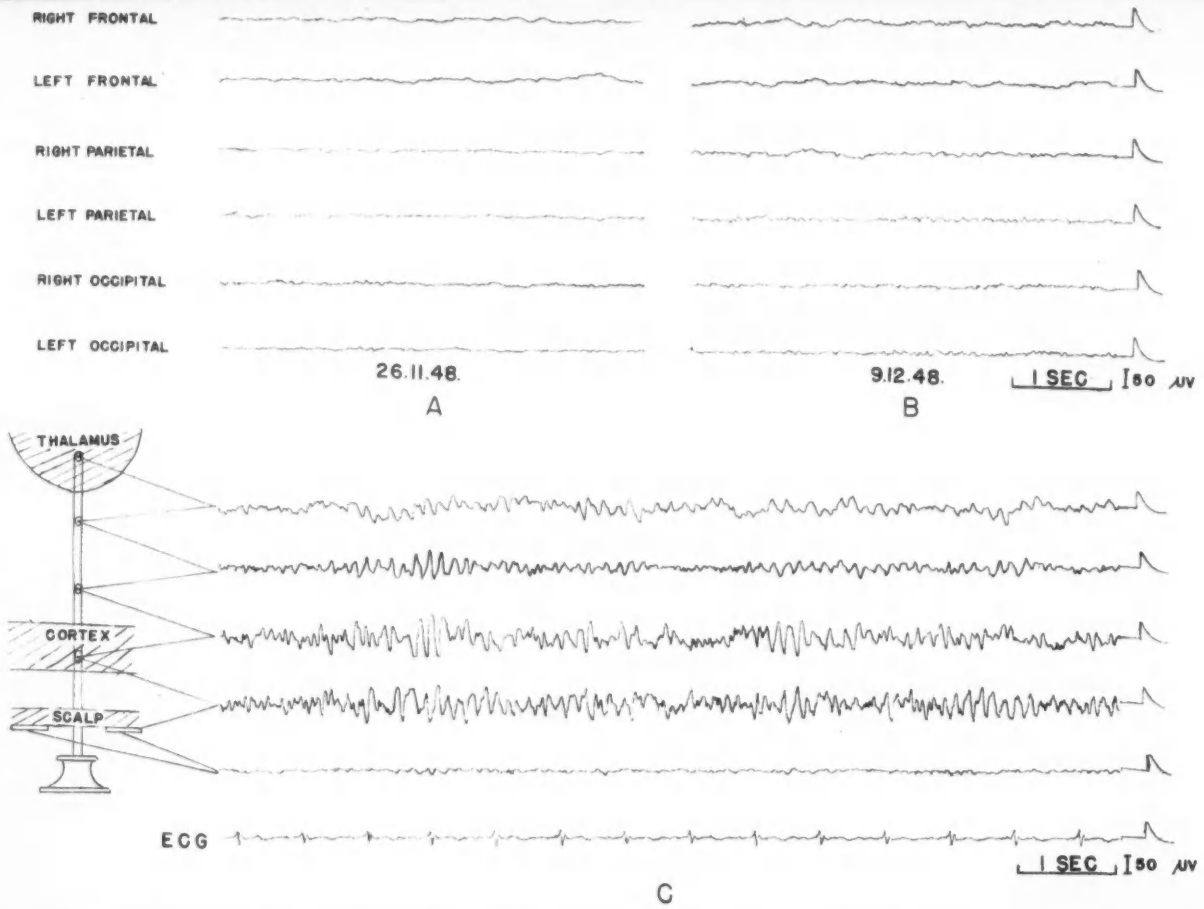


FIG. 5 (*Case* 2).—Examples of electroencephalograms made with the standard technique on different days are shown in A and B. The records are seen to be relatively featureless. In C records made with the needle electrogram are compared with the E.E.G. The rhythms arising in the cortex are only just evident in the E.E.G. although the recordings are identical for all the records, with the exception that the interelectrode resistance is much lower for the scalp than for the cerebral records. In the cortical and subcortical leads 8 a second rhythms with a voltage of 100 to 150 μv. can be seen to arise in the cortex and to spread deeply. Underlying these rhythms are runs of 16 to 18 a sec. -1 frequencies which are not seen in the thalamic leads. The ' -imultaneously, is similar to the examples in A and B.

rhythm of high voltage (100–150 μv.) with a frequency of 4 to 5 a second, disturbed from time to time by slower waves of a higher voltage (200 μv.). These slower waves ranged from 1 to 4 a second. They had a smooth contour but a complex wave form. These rhythms and random waves arose in the cortex, as shown by phase reversal (fig. 3) and by their amplitude on withdrawal of the electrodes from the brain 1 cm. at a time. They did not reach the optic thalamus, in which the terminal electrode was initially placed. On the contrary the thalamic records were, as is seen, relatively featureless and showed no characteristic rhythm. Examples of these phenomena are seen in figs. 3 and 4. It is important that the resistance between the large surface electrodes was only three thousand ohms, while that between the minute needle electrodes was one hundred thousand ohms.

Case 2.—A man aged 63 had had about four major fits each year for forty-five years. In the last year he developed a steadily increasing dementia together with a progressive left hemiplegia. On examination there was a mild spastic tetraplegia more marked on the left. He had severe arteriosclerosis. Investigations were all negative except that a ventriculogram showed large ventricles with evidence of cortical atrophy.

The electroencephalogram recorded on two occasions was normal. It showed a dominant frequency of 11 a second with a very low voltage (fig. 5A and B) and a normal distribution. No abnormal rhythms were seen and the response to over-breathing was normal. The records were virtually flat. Needle electrographic records were made and are illustrated in fig. 5C. They showed that at a time when the E.E.G. was featureless high voltage (100 to 150 μv.) 8 a second potentials arose in the cortex and spread deeply. Underlying these rhythms were frequent runs of 16 to 18 a second waves which did not spread to the thalamus, and which were also not seen in the E.E.G.

In the first of these two cases abnormal rhythms and random waves of high voltage ranging from 1 to 7 a second arose in the cortex, but were not evident in the electroencephalogram. In the second, rhythms with a frequency of 8 a second and a high voltage were similarly evident in the needle electrogram but not in the E.E.G. *They show that records made from electrodes on the scalp may not represent the spontaneous rhythms arising in the cortex.*

The surprising discrepancies described in these two patients might be the result of instrumental factors, but we have done our best to eliminate this possibility. In particular the resistance between the cerebral electrodes was always much higher than across the scalp, the scalp electrodes were much farther apart, records were made from electrodes below the bone, amplification was altered, and recording channels were interchanged. *In any case the point under discussion is that electroencephalograms recorded with standard techniques may bear little resemblance to direct recordings from the substance of the cortex.*

Discussion

Although the frequency and form of spontaneous waves of electrical potential arising in the cortex have been extensively studied little is known of their methods of propagation and some known facts are quite unexplained. For instance the "wave and spike" discharge seen with *petit mal* may in some cases be recorded quite synchronously from all points on the scalp, a finding which might suggest that the wave complex arose deeply, but which has not so far been explained satisfactorily. Again, although some rhythms seem to spread over the scalp so rapidly that their propagation can only be explained on the basis of electronic conduction, others spread very slowly, and some have seemed to follow the line of the major gyri. Adrian and Mathews studied the spread of the alpha waves over the human scalp in 1934 and found rather a slow centrifugal propagation. Although Dusser de Barenne and McCulloch (1936) studied the level of origin of rhythms within the cortex by means of progressive thermocoagulation, there seems to have been no study of the spread of the rhythms through the depth of the cortex instead of over its surface.

Work from several laboratories in recent years has shown that the focus of interest is moving from the study of the cortical potentials to those rhythms which may occur within the subcortical structures. Thus Walter and Dovey (1946) studied the frequencies which occur around subcortical tumours with a needle electrode. Lennox and Ruch (1946) recorded ventricular electrical activity in three human cases and in thirty monkeys by means of buried wire electrodes in the lateral ventricle, and considered that the ventricular electrical activity usually parallels cortical activity. Under certain conditions, however, they found that unipolar and bipolar recordings were entirely different from the cortical activity. They assumed from this that the ventricular lead records the electrical activity of the surrounding subcortical structures and not that of the overlying cortex. Other workers too have described differences between the frequency of the cortical potentials and those obtained from the deeper structures. Meyers, Hayne and Knott (1949) investigated the electrical activity of the basal ganglia in parkinsonism and hemiballismus. They noted that in parkinsonism the frequencies which were derived by bipolar technique from the corpus striatum were very variable and that they were often faster than those recorded from the scalp leads. In some cases runs of fast activity were recorded which appeared to arise from the dorsal half of the caudate nucleus. Similar runs were not seen among a group of control subjects. Gastaut (1949) has, like us, described discrepancies between the E.E.G. and records made from electrodes 9 mm. apart within the subcortical white matter of the occipital lobe in man. He has also compared unipolar and bipolar recordings of the intracerebral potential changes. He describes an increase in the voltage of the subcortical records compared with the E.E.G. and he comments that the subcortical records may be very different, having faster or slower waves

than those seen in the E.E.G. He also suggests tentatively that the fundamental difference may be due to the fact that the subcortical records are taken in a plane radial to the surface so that they record activity from closed cortico-thalamic circuits orientated radially to the surface.

It seems from the observations recorded here that rhythmic potential changes arise in the hemispheres, apparently within the cortex, which are propagated upwards and downwards within the depth of the cortex. This propagation is demonstrated by phase reversals which can be obtained. These rhythms reach the white matter and spread in it but are not readily recorded from the basal grey matter. They are not picked up by two electrodes placed along the surface of the brain. The obvious inference is that they reach the surface synchronously in all positions and so do not cause a potential change there. It would be unwise to draw such a definite inference from this unexpected observation at this stage, but it certainly raises many interesting points relating to individual variations in the E.E.G. It is known, for instance, that the voltage of the normal "alpha" rhythm recorded from the scalp is not dependent alone on tissue resistance, and the apparent absence of this rhythm in some subjects has not been explained. Some epileptics (as in Case 2) do not show any dysrhythmia in the E.E.G. and there is often a lack of relationship between the degree of abnormality seen in the E.E.G. and the severity either of the manifest epilepsy or of the degree of epileptic inheritance in any one patient. It may be that in such cases many abnormal rhythms and waves of electrical potential change are arising in the cortex which are not available to the E.E.G. Finally there is sometimes a disparity between the degree of abnormality seen in the E.E.G. and the clinical expectation of local abnormality. As Walter and Dovey (1946) stated, this can be studied by needle electrography and it now seems that further information may be obtained by recording through the substance of the cortex.

Summary

(1) Two examples are described of records made from electrodes inserted in the brain across the cortex which have been compared with the E.E.G. Normal rhythms, abnormal rhythms and random wave complexes, all of high voltage, arose in the cortex but could not be recorded from the overlaying scalp using accepted electroencephalographic techniques.

(2) In some cases the electroencephalogram does not reflect the electrical potential changes arising in the underlying cortex. This fact can be related to the individual variations and anomalies which have been observed in the E.E.G.s of some normal and abnormal subjects and it requires further study.

(3) A possible explanation of the absence of potential changes at the scalp when marked rhythmic changes can be recorded through the underlying cortex is that the potential changes are occurring through the depth of the cortex from many points but reach its surface synchronously.

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A CASE OF AUDITORY AGNOSIA

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As sensory data, or sensa, sounds are the product of stimuli which consist in movements in the air.

Sounds do not enter consciousness ordinarily without having undergone some measure of integration and interpretation. They are perceived as musical, as vocal, or as derived from some mechanical source, such as a machine. That is to say that auditory sense reception pure and simple is exceptional; what is in question is sense perception. Sounds come into the focus of attention as spatialized, and identified as to their source and significance. This perception, which has its physiological and its psychological elements, has also affective accompaniment. It follows that auditory perception as thus considered is a product of experience, and this in turn depends upon the culture, conventions, language and general environment of sounds in which the individual has lived. Sounds without significance to the recipient can be heard only by the infant, or later in life when they are wholly unlike sounds heard before and cannot be contrasted or compared with previous auditory experiences, for we perceive by the method of contrast. Such undifferentiated hearing is pure sense reception and not sense perception.

Further, certain Eastern music has an unpleasing and discordant affective quality for Occidentals, while foreign languages lack symbolic value to those who have not heard them before. It is also possible that certain sounds are unpleasant for all human subjects alike (Fry, 1949).

This may have no relation to the association they carry, but because the auditory receptor organ is ill-adapted to them. In a sense they may be said to belong to the category of nociceptive stimuli.

Should there be some defect in the process of selection, differentiation and integration of auditory stimuli, while the mechanism for receiving them and conducting them to brain tissue remains intact, the condition of auditory agnosia results.

A person with auditory agnosia suffers from an inability to hear sounds in the same way that normal individuals hear sound. Some fault has occurred during interpretation of the auditory stimulus and the resulting sensation of sound has a quality which is different, in the patient, from the sound which a similar auditory stimulus would produce in a normal person.

If a lesion has occurred to produce auditory agnosia after the process of learning the accepted significance of sounds is completed, auditory

stimuli may result in subjective sensations which are quite meaningless to the patient. The sounds do not resemble anything he has previously known.

Defective interpretation may be congenital.

Although it is probable that the whole cortex is involved in the interpretation of auditory stimuli, patients have been described in whom, as the result of injury, only a single "category" of sounds has been affected. Thus only spoken words have been affected, or music alone, while the other sounds are normally heard. It is possible that many other specific integrations of sound patterns exist. At the present time, however, one may regard only two categories of sounds as having qualities which permit their individual isolation, "verbal" sounds and "musical" sounds. All other sounds must be included in a single category.

Word deafness, or the inability to understand the accepted content and symbolic meaning of word sounds, has been frequently recorded in medical literature. Bastian in 1869 was among the first to discuss the condition. Since that time numerous cases have been described, notably by Wernicke (1874), Lichtheim (1885), Pierre Marie (1917), Henschen (1920), Goldstein (1926), Stengel (1940), and others.

The condition has been described by these authors as an isolated disability, or else occurring with other specific defects, as aphasia, alexia, agraphia, amusia, akopia, etc. Stengel and Hemphill (1940) have described a patient who suffered from word deafness with asymbolia for pain.

The disturbance in the interpretation of sound called amusia has been fully discussed by Henschen (1920) who considered that "rhythm is the principal constituent factor in music. The second essential factor is pitch. In addition to these basic requirements, melody, modulation, intonation and accentuation are required to produce music." A more modern contribution to the study of amusia was made by Feuchtwanger (1930). This author was interested in the problems of auditory perception and musical production and in the interrelationship of music and speech. He noted the clear differentiation between expressive and receptive disorders and could make further distinctions in each group. He considered that not only hearing itself but the more highly organized auditory experiences in both speech and music involve bilateral cortical activity. He reported in detail 2 cases of amusia.

Henschen (1920) quoted a case of Wortzen describing amusia occurring in a "ballet dancer and excellent musician aged 48, who suffered a stroke and, as a result, a temporary left-sided hemiplegia. General mentality and understanding were scarcely affected, but comprehension and expression of music were strikingly affected: his rhythmic sense had entirely disappeared. He failed utterly to beat a measure or to keep time in dancing. He had no insight into these mistakes. Notwithstanding, he greatly enjoyed listening to music. Energetic attempts to relearn music met with failure. He was unable to recognize false notes when he played.

In this case rhythmic sense was affected as well as judgment of pitch." (Schaller's translation.)

Henschen also mentioned that musical memory may be completely lost, but emphasized that emotional stimulation, even to a mild degree, can overcome musical amnesia. He suggested that this would point to an automatic mechanism of song, but Goldstein (1927) believed that where singing is an activity closely connected with the patient's affective life, it is likely to be preserved when speech is lost. Under such conditions, the song is not "representative speech," but an expression of feeling, like a prayer (Weisenburg, 1935).

The impaired interpretation of all sounds was mentioned by Morel (1935) who quoted Pierre Marie and Foix as having stated that "the loss of hearing of all sound which is sometimes called psychic deafness never appears alone. It always accompanies either tone deafness or word deafness or both."

It is suggested that "deafness" is an inappropriate term for the condition which consists of an altered appreciation of sounds, but not a loss of appreciation of sounds. The patient here to be described suffered from lesions affecting the interpretation of all sounds including speech and music. While it is true that specific functions of the human brain may be partially or totally destroyed, it is unlikely that any single lesion in the cortex, however sharply defined, can be present without affecting many cortical functions. Each separate function is the result of a constant synthesis of many processes, highly organized, widely associated and diffusely situated in the cortex.

Our patient showed a number of abnormalities of brain function apart from the specific ones mentioned above. Some of these, such as impairment of memory and capacity to write, were the direct result of the specific defect. Others were of a more general nature.

Memory is dependent upon the interpretation of sensory stimuli. As previously stated a stimulus must be transformed into a sensation before it can be appreciated by the individual. The brain is able to retain sensations in the form of "images" of those sensations. This patient suffered from a faulty interpretation of auditory stimuli, and had, as a direct consequence, imperfect images, and a defective auditory memory.

Writing is as a rule learned later than speech. Until recent years, most people were taught to write according to the sound, rather than the appearance, of letters and words. It is likely, if this is the case, that writing is affected by preliminary auditory associations. Certainly our patient's writing was the recorded image of her speech (*see* tests).

History.—The story of the onset of the patient's disability and her past history were obtained from her mother, the patient herself having a confused and defective memory, and little insight into her condition. The patient was born in Italy in 1916, the youngest child of a French mother and an English father. Her mother had had five previous pregnancies in quick succession, and two of the children had died at birth. Of the remaining children, only the patient and one sister survive. One boy died of an obscure fever at the age of 14 years; another, a girl, died as

the result of a tumour of the brain at the age of 13 years. The patient was born by normal delivery at the end of a normal pregnancy. She was a healthy, breast-fed infant, and sat up, walked, and talked at the normal ages.

The family left Italy in 1922 and came to England, where the patient has since lived. The family life was stormy and difficult, complicated always by poverty, and at various times by the illnesses and death of the two older children. The patient's ageing father was of stern character, unsympathetic to failure, her mother extremely capable, energetic and frustrated. On arrival in England the patient was sent to school, and there for the first time was noticed to be somewhat backward. Her mother denied, however, that there was any marked defect, except a weakness in arithmetic.

School must have created difficulties for the patient, and her inability to cope with it resulted in what was called a "nervous breakdown" at the age of 12. She had to be taken away and rested for six months. After this she went for some time to a school for backward children.

She was then 14 years old, and she left school to do a Pitman course of shorthand and typing. Here she did not distinguish herself, and after about a year she gave up the course, and began a variety of other occupations. She was in the book department of a church missionary society, then took up sociological work and became interested in child welfare. She then took a course in Montessori training and acquired the Diploma. She began training as a nurse, but gave this up when she failed to pass the examinations. During the war she joined the A.T.S., and did secretarial work. She also drove lorries at one time and worked on a telephone exchange for six weeks. She obtained her discharge on compassionate grounds after three years in the A.T.S., on account of her father's death in 1946. She returned home and worked for a while in a soldiers' canteen. It was then she began for the first time to complain of feeling unwell. She suffered from headaches and was noticed to vomit frequently. She was seen by several doctors but no diagnosis was made. She continued to work and in 1947 was engaged in a doll-making factory. She disliked this work very much but remained at it for almost a year. Towards the end of this time she was noticed to be behaving strangely. It seemed she was talking nonsense and did not understand what was said to her. Such behaviour continued for about two weeks. She went one afternoon for a long walk alone, came home, was sick, seemed ill, screamed, wept, went to bed, and next morning, on waking, was "deaf and dumb." Then words came back and she said "all right" over and over again.

She was admitted to the Hampstead General Hospital where she grew worse, her mother said, and did not recognize anybody. Shortly afterwards she was removed to Napsbury Mental Hospital where she remained for nine months. On admission, she was suffering from auditory hallucinations. She was diagnosed as a schizophrenic. After several months of confinement, she was recognized to be suffering from a defective understanding of speech. She was discharged with the diagnosis of "word deafness," and later sent to the Out-Patient Department of the National Hospital in order to ascertain whether the learning of lip-reading was likely to be of assistance to her.

It is interesting and important to note that throughout her life the patient had a great variety of interests apart from school and work. She was passionately fond of music, learned to play the piano and sing. She continued to practise the piano at the time of this examination—although unable to afford lessons.

She was "clever with her hands," liked to embroider, to draw, to knit, to cook, take photographs, and also to cycle and swim. She read a great deal. She had many pen-friends in a number of foreign countries. She was a member of the Y.W.C.A., and performed charitable social works whenever she had an opportunity to do so. She greatly enjoyed travelling and sight-seeing.

She was, however, always of a quiet, reserved character, had few friends, and " never told her mother anything," the latter complained.

During the war and in the years that followed, the patient was rather isolated from her family and even when she lived with her mother after her father's death, the two, having different occupations all day long, saw little of one another.

The patient thus appeared to have been a shy, somewhat withdrawn girl, perhaps mentally backward in certain directions, forced by necessity to earn a living, however unpleasant the circumstances, pursuing at the same time a variety of interests, contending with an environment of change, insecurity, poverty and frustration.

At the time of examination, the patient was 33 years old. She was a slight, dark woman, with a timid and anxious expression. She dressed neatly, curled her hair, wore bracelets and brooches, this indicating a certain vanity and care. In the first moments of acquaintance she might have passed for a normal although not very intelligent person, with a tendency to a lengthy and irrelevant response to questions.

After a few minutes' conversation, however, it became clear that the patient understood the content of almost nothing of what was said to her and that her monopolizing monologues were used to conceal this fact, and distract attention. Even more surprising was the later discovery of the fact that the patient was quite unaware of her defect, and entirely lacked insight into the reason for her side-tracking manœuvres.

She talked in a soft voice, her sentences correctly formed and phrased, with a normal cadence and rhythm of speech. Occasionally she hesitated slightly, made small mistakes of pronunciation or tailed off into a vague blur of meaningless sound. Whenever possible she talked without a break, earnestly, quietly, and she never, in all the weeks during which this examination took place, asked a single question.

Having confirmed the fact that the patient could not understand the content of, nor correctly repeat, spoken words, further tests were performed, from which it could be concluded that all sound had for her distorted meaning, and that she was quite unaware of her defect, although the mechanical reception and transmission of sounds, as careful examination showed, was unimpaired.

Testing revealed she had a perfect comprehension of the written word and that she was able to read both aloud and to herself, although the content of what she had read was sometimes incompletely grasped. She could write well, although grammar, punctuation, and spelling were curiously disturbed. She had no dyspraxia, nor any other form of agnosia.

Examination of the central nervous system showed no abnormality.

A diagnosis of hysteria might have been justified were it not that the patient showed in addition to the strangely isolated (yet not absolute and unvarying) false comprehension of sound, the signs of a more diffuse disturbance of cortical function.

The patient demonstrated a marked disturbance of " categorical " or " abstract " thinking (Goldstein). She was able to focus attention at a given moment upon a single object only. She had defective understanding of the symbols used in arithmetic (+ × —) and punctuation. She had moulded her life into a complicated " milieu," or pattern of behaviour so as to conceal her defects, avoiding other persons and distracting attention during conversation in an attempt to appear normal. When exposure seemed inevitable however, she became distressed and gave signs of the " catastrophic reaction " (Goldstein).

As speech was an entirely unprofitable means of communicating with the patient, although writing was perfectly understood by her, all further contact was established by means of pencil and paper. The patient expressed no surprise at this written conversation, in fact, seemed glad of it and often herself preferred to write down her answers to questions rather than speak them aloud.

Hearing.—The patient was first carefully tested by Mr. Cawthorne, the aural surgeon. It was impossible to obtain an audiogram because the patient failed to grasp the principle of the test, and in any case, being unable to perform two functions at once, could not both listen to the sound, as well as give a brisk indication she had heard it. Also she was very inaccurate (she often said she had heard a sound even when none was given simply because she believed she was expected to have heard one), and extremely slow in her replies. In spite of this failure, however, Mr. Cawthorne was reasonably certain she could hear the whole range of frequencies of sound, and stated "There is no evidence of any lesion in the sound-conducting or sound-receiving part of the auditory mechanism."

The tests now to be described in detail illustrate the patient's special defects. Throughout testing, signs of the more general deterioration can also be noticed.

A brief and typical conversation between the examiner and the patient is here recorded.

Q. Good morning! How are you today?
A. No I didn't because I thought you would understand. I had a cold. I've brought my music with me.
Q. Is your cold better?
A. I'm going down to the Studio at 5 o'clock.
Q. Would you like a cup of tea?
A. Oh, if it weren't for my cold I'd feel perfectly well.

(1) *Sound Interpretation.*

(*a*) *Word sounds.*—The patient was asked to repeat aloud certain words spoken to her. Some of the words and her responses are given:

Word	*Patient's attempt at repetition*
Book	Work
Ruler	Were you?
Pearls	World
Decision	Were you—did you?
Business	Were you?
Tooth	Cook—I can cook.
Pressure	Pleasure, when I went to Blackpool it was Pleasure Ground.
Skirt	Were you a clerk?

Occasionally the patient made incoherent noises in her attempt at repetition of a word, then struggled through to a quite unrelated word and launched upon an anecdote, e.g.

Necklace	net, and—ended—Netball, I play netball, etc.

It will be noticed that the patient often realized the correct rhythm and emphasis of the word and the number of syllables it contained, especially in a short word, e.g. for *book*, said *work*, for *ruler*, said *were you*, for *tooth*, said *cook*, etc.

During such testing, it was noticed the patient fixed her gaze with intense concentration on the examiner's face, and it was found she was able to lip read to a certain extent. When the examiner's mouth was covered she had even greater difficulty with conversation.

It should be noted that no nominal dysphasia existed—as shown by later testing.

The patient was better able to understand words said to her with which she was daily familiar, e.g. her address, "West Hampstead"; and the word "mother," always seemed to be understood by her. As regards the understanding of her own

speech, the patient made small mistakes in talking, which she did not correct, presumably as she did not perceive them. She was asked to whisper. She at first made movements of her lips without any sound issuing, but, after a few moments, suddenly began to whisper.

(*b*) *Music.*— The patient had, in the past, been an ardent pianist, and continued to practise the piano alone at the time of examination. It was found she was able to read music, although this very haltingly and at times incorrectly, and could play the notes on the piano while the music was before her. She was also able to play from memory a very simple piece she had recently learned. She was, however, quite unable to recognize differences of pitch, had no understanding of rhythm and was incapable of recognizing tunes played to her with which she must previously have been familiar, e.g. " God save the King," " The Blue Danube," etc.

Test : Two separate notes were played, sometimes the same note repeated, sometimes two different notes, e.g. B and C. The patient was quite confused as to whether the notes played were the same or different. She called two like notes " different, one higher than the other." She called two different notes " the same note repeated twice." She appeared uncomfortable during this test saying she had " forgotten most of her music although she used to play very well," changed the subject frequently, turned the pages of her music and attempted to distract the examiner's attention in many other little ways.

(2) A simple rhythm was played repeatedly on three notes — · · — · · — · · — · · She was asked to reproduce it. She could not do so, playing a series of notes in no form of regular rhythm.

(3) " God Save The King " was played to her. She said she could not recognize the tune. " The Blue Danube " was then played. She could not say what it was. Asked " is it a waltz ? " she said " It's *not* the Blue Danube."

Similar tests were performed with song. The patient failed in the same way to recognize differences in tone, pitch and rhythm, and to recognize well-known tunes.

The patient was asked to write some simple notes on a blank score, e.g. a, b, c, e, f, d. She made a few mistakes but on the whole was accurate as regards position

FIG. 1.

of the note, but at times reversed the note symbols—as in a mirror writing (e.g. as above). She knew the symbols for " sharp " (♯), but at times reversed the symbol for " flat " (*d* for *b*).

The patient was asked to sing. She would only do so if the written words of a song were given to her, and she then began to make strange unmusical sounds, bearing no relation to the correct tunes—even for hymns with which she was very familiar.

The patient thus showed no defect of the motor function concerned with music. She could make the movements for singing, playing the piano, and writing a musical score. She showed no " note blindness." She suffered, however, from defective interpretation of musical sound, with a defective musical memory. She showed a defective understanding of rhythm, tone and pitch.

(*c*) *Interpretation of sounds other than speech.*—The patient's eyes were covered and she was asked to identify various sounds made in her vicinity—e.g. keys rattling, paper crumpling, shaking of a matchbox, a clock ticking and the ringing of

a telephone. The patient only rarely identified the correct sound, and seldom associated it with its origin. She called most noises " rattles " or " squeaks."

For example : *Crumpling of paper*—The patient said " squeaks." Asked what caused the noise she could not say. Her eyes were uncovered and she was shown the paper being crumpled. She smiled and said " paper." Her eyes were again covered and the noise was repeated. She now called this a " rattle " and could not explain its origin.

Keys rattling—The patient called this " a rattle " and the procedure and her performance were similar to that described above.

A telephone bell ringing immediately behind her she called " Furniture being moved in the next room." She said the ticking of a clock " sounded like the wind."

It was noticed that when sounds occurred outside the radius of two feet from the patient she was very vague and inaccurate as regards their localization.

The patient failed to exhibit a startle reaction. Doors were suddenly banged, hands loudly clapped above her head, heavy objects dropped with violent clatter beside her, and she gave no indication of disturbance. The absence of startle was only to be expected, as sound symbol was altered for the patient. She reacted, however, to other forms of sudden stimulus, e.g. pin-prick, and showed no asymbolia for pain.

Further tests of auditory appreciation were performed. The most concise illustration of the patient's defect is given by the rhyme test. It was established that the patient understood the meaning of the word *rhyme*. She seemed at once to recognize this word and appreciate it, laughed, and said " I'm no poet, I hope you won't ask me to write poetry." Several examples of rhyming words were shown to her. She was then asked for words rhyming with given words, e.g. for

Tree	the patient wrote	*Trees*
Pig	the patient wrote	*Fig*
Cat	the patient wrote	*My pet*

She was then given a number of passages which she was asked to read aloud and to pick out the rhyming words. Although she read correctly she was able to pick out rhymes only when the rhyming words had identical spelling, e.g. *cold* and *gold*. She could not detect rhymes in *although*, *hullo* and *know*, where the spelling of each word is very different, even after reading them aloud several times. She always said that words of identical spelling were rhyming even when this was not the case, e.g. *mouse* and *blouse* ; *crow* and *brow*. She correctly read and pronounced these words aloud.

It can be seen here how the patient used her other faculties, e.g. reading and spelling, in her attempts to preserve normality.

Finally the patient was asked to copy simple rhythms that were tapped out for her with a pencil on a wooden table. She entirely failed to tap anything resembling the given rhythm, although, obliging as ever, she tapped for some time in a meaningless manner.

Auditory memory.—The patient was unable to recognize words and tunes with which she had been previously familiar. The defect was one, however, not so much of memory as of interpretation. Words and tunes were interpreted by the patient in an inconstant fashion, seldom related to a previous interpretation. The resulting subjective sensations of sound were therefore quite unrelated to sounds previously heard, although the original stimuli were constant.

When objects were presented to the patient together with their spoken names, the patient was perfectly able to repeat the names correctly, e.g. book, bag, pencil. She was asked to remember the names. Later the objects were removed from the patient's sight. She was asked to recall the three names. She was able to do so without hesitation. This test involves, of course, visual and auditory sensations and is not satisfactory.

Insight.—Very early in the examination it became clear that the patient lacked insight into her defect. When encouraged, she entered whole-heartedly into conversation, without giving the least indication that she could not understand what was said to her. She was entirely unaware of the irrelevancies of her replies.

When directly questioned regarding her understanding of speech she made excuses and hedged, e.g.

Q. " Have you any difficulty in hearing what people say to you ?"
A. " It depends."
Q. " Do you always understand what people say to you ?"
A. " One can't always judge what people say ; they all have their own pronunciation."
Q. " Is the understanding of words your chief difficulty ?"
A. " Never had any real trouble."
Q. " Can you hear yourself speak ?"
The patient made no answer.
Q. " Do you sing in tune ?"
A. " Yes, of course."

Throughout the weeks that followed, the patient gave no sign that she recognized her defects. She kept up a constant agitation that " she must find a job," haunted, as ever, by financial difficulties, going so far as to cut out, and reply to, advertisements in the daily paper.

She seemed entirely unaware of the fact that she was incapable of performing any work, although even the simplest tasks in the occupational therapy department, where attempts were made to employ her, baffled and defeated her.

Spontaneous speech.—This was almost normal, as previously stated, although sometimes words were left unfinished. Sometimes words were mispronounced, and occasionally the patient tailed off into a meaningless blur of sound. She spoke as a rule in a soft rather monotonous voice, but used correct emphasis, phrasing and cadence. In ordinary conversation her vocabulary was not noticeably diminished, although special testing revealed a poverty of words.

Naming of objects.—The patient named correctly various objects shown to her, e.g. pencil, wrist-watch, grass, keys, powder-compact, nail file, mirror. There were a few objects she was unable to name, presumably unfamiliar to her. She did not say " I don't know what that is," but unhesitatingly called the object by a wrong name, e.g. for " orange-stick " she said " *pencil.*" It is suggested this is in accordance with her general lack of insight and inability to admit defeat.

Naming of colours.—No colour agnosia was detected but here the patient showed extremely clearly the quality of " concreteness " relating all colours to the objects they qualified. Frequently she mentioned the object first, then the colour. For example, asked the colour of a white blouse, the patient said " That's a blouse, a white blouse, long sleeves." Similarly she spoke of a red *dress*, blue *bag*, green *grass*, blue *sky*.

Reading.—The patient could read accurately, with correct intonation, phrasing and punctuation. She made rare mistakes of pronounciation of words. As regards her comprehension of the content of what she read, she could perfectly reproduce the exact meaning of certain words and paragraphs, but she lacked the ability to grasp concepts. Here again she showed the tendency to relate everything to concrete objects.

The patient was asked to read and define words and to read, aloud and to herself, paragraphs and proverbs, and give their content. Some of the words are quoted, together with the patient's definition of them. The latter demonstrates also the faults in her spelling which are, however, discussed in detail later.

Word	*Patient's definition (written)*
Orange	Fruit with pips
Precise	Title
Aware	Danger
Principal	Tutor
Shadow	Shade in the sun
Reflection	Shaddow—Double
Image	Idol
Justice	J.P.
Mystery	Hidden Treasure
Joke	Laughter
Abstract	Vacant
Goodness	House of Lords

She was then given some proverbs to read and asked for the meaning of them, for example :

A burnt child fears the fire—" Frightened of being burnt."

Once bitten twice shy—" Once tried not to try again—not always."

She was given the fable of the Fox and Grapes to read, and asked the meaning of it. She wrote " The fox couldn't jump high enough to get at the grapes, he continued to jump, we are all like that, in life there are always barriers."

The patient was an avid reader of novels belonging to a library and was often talking of and recommending the books she was reading, e.g. " The Spirit of India," a travel book, " Human Destiny," by a French Philosopher, " Immortal Village," by Donald Peattie.

Writing.—The patient made mistakes in her writing similar to those she made in speech.

The general impression of the written words was normal, there being nothing strikingly unusual in the appearance, character and distribution of the symbols and words on the page. Closer inspection, however, revealed numbers of unfinished words, slipshod spelling, and a very strange and erratic use of capital letters and punctuation. Occasionally the verb was omitted in the sentence.

When uncertain of the correct spelling of a word she would write it with the same vague hesitancy as she showed in pronouncing an unfamiliar word, and this can be clearly seen in the soft, formless nature of the characters.

Spelling.—The patient stated she was good at spelling. It was difficult to test spelling, as the dictated word was distorted and meaningless to her. Other methods of testing spelling were, however, used.

In both spontaneous writing and during testing, the patient made many spelling mistakes. The greater part of these was probably due to carelessness. Others, where the spelling was hopelessly wrong, would perhaps not have been as gross in a person who had the use of speech to correct phonetically the mistake. The patient had to rely, in her spelling, upon past experience and present associations with written words.

Tests :

(1) *Dictation.*—Patient was asked to spell " cat "; she wrote " but that."

(2) *Objects* were then shown to her and she was asked to write them down. A few typical mistakes are given :

scissors	sciccors
mirror	mirrow
bracelet	braclet

Spontaneous writing showed mistakes such as :

tireying	for	tiring
devoloped	for	developed
nurvouse	for	nervous

Examples of patient's writing

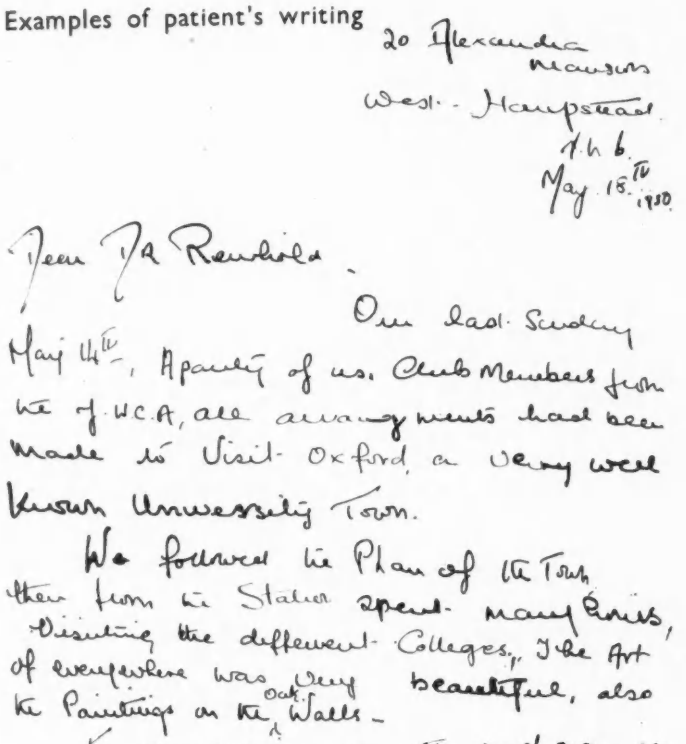
20 Alexandra Mansions
West - Hampstead
N.W.6.
May 15th 1930
Dear Dr Rowbotham.
Our last Sunday
May 4th, A party of us, Club Members from
the Y.W.C.A, all arrangements had been
made to visit Oxford a very well
known University Town.
We followed the Plan of the Tour
there from the Station spent many hours,
visiting the different Colleges, The Art
of everywhere was very beautiful, also
the Paintings on the Oak Walls -
In the evening we attended an even-song
Service in the Christ Church Cathedral.

FIG. 2.

When trying to write "Streatham," the patient made a few attempts which she crossed out and finally achieved "Streathrman."

Punctuation.—It had been noted that the patient's use of punctuation marks and capital letters was very erratic. In *spontaneous writing* capital letters were inserted haphazardly, usually for emphasis, e.g.

"my Mother Rejoined me; owing to Blindness . . . . . ."

The punctuation marks bore little relation to the content of sentences, e.g. "My brother was very brilliant; at school, but developed Scarlet Fever on holiday and then died in Hospital at Brentwood; 4 years later; then the other one."

The patient was accordingly tested as to her understanding of the symbols of punctuation and as was to be expected these had little meaning for her. She was also asked to punctuate several paragraphs. An illustration of her performance is given below.

Paragraph given:

> i heard a story yesterday said john about three dogs called sarah henry and joseph they all went down to the river and what do you think they did

The patient punctuated the above thus :

> " i heard a story yesterday said john about three dogs ; called sarah Henry and Joseph. They all went down ; to the river and what do you think ? they did, Fishing.

Other symbols were then tested. The patient could write the alphabet in small and capital letters and numbers from 1 – 20. The mathematical symbols of +, ×, —, =, were given to the patient. The patient recognized +, and —, but invariably called × plus, and = minus, and all sums worked out accordingly, e.g. 7 × 3 = 10.

An attempt was then made to play the game of noughts and crosses, a game which the patient appeared to recognize and stated she had played many times in the past. The attempt proved unsuccessful. The patient did not understand :

(1) That she could use either a nought or a cross, but not both indiscriminately.
(2) She failed to grasp the conception of the purpose of the game. Some examples of play are given :

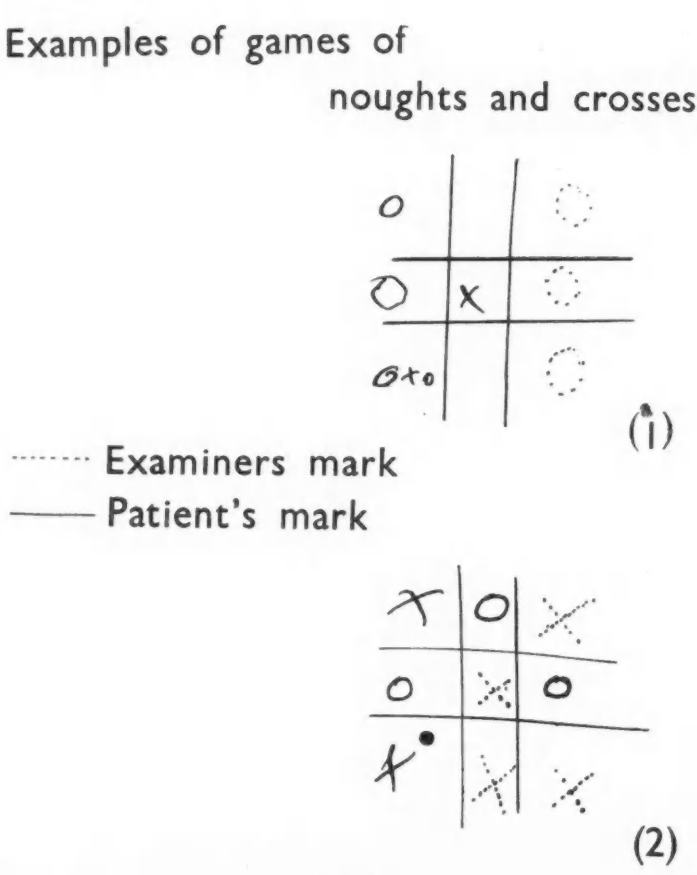

FIG. 3.

Another example of a defective understanding of symbols was seen in the Clock test. Although the patient could tell the time perfectly well when reading it on an actual clock face, when she was asked to insert hands showing a certain time in a clock drawn on a page with lines but no figures, marking the hours, she failed completely to do so, for example :

The patient was asked to put in the time, twenty to five. She did this :

FIG. 4.

This test was repeated over and over again, with different times to be inserted. The patient was quite unable to approximate, however inaccurately, to the correct time, but was always completely wrong. When asked to read back the time she had shown she was unable to do so. It thus seemed that there was a defective understanding of symbols or ciphers, under certain conditions.

Calculation.—Apart from her lack of understanding of arithmetical symbols, the patient was able to do only most simple calculations, and those very slowly. There was, however, no true acalculia, her difficulties being due rather to defective conceptual thinking. Acalculia is, of course, in itself a specific defect in conceptual performance.

Visual memory of patterns was tested at the same time as praxis. The patient could correctly remember designs that could be described in terms of concrete shapes—e.g. a box within a box, a circle, a triangle, but when the designs given to her could not be so described, she failed completely to remember them.

The patient was unable to focus her attention upon more than one object at a time, thus the attempts to do her visual fields on the perimeter and to obtain an audiogram were unsuccessful. Similarly it was found in a simple test in which she was asked to recite the alphabet aloud and at the same time copy a drawing of a triangle she was unable to perform the two tasks simultaneously. She was, however, able to copy the triangle while reciting numbers 1–20. She could recite the numbers more easily than the alphabet. The inability to perform two tasks at once obviously depended upon the difficulty of the tasks involved.

Orientation in space and time.—The patient could give the day of the week correctly, and knew where she was. She could find her way correctly in the streets, take the right buses and quickly learnt her way about the hospital. She could tell the time correctly from a clock and was correctly orientated regarding time of day,

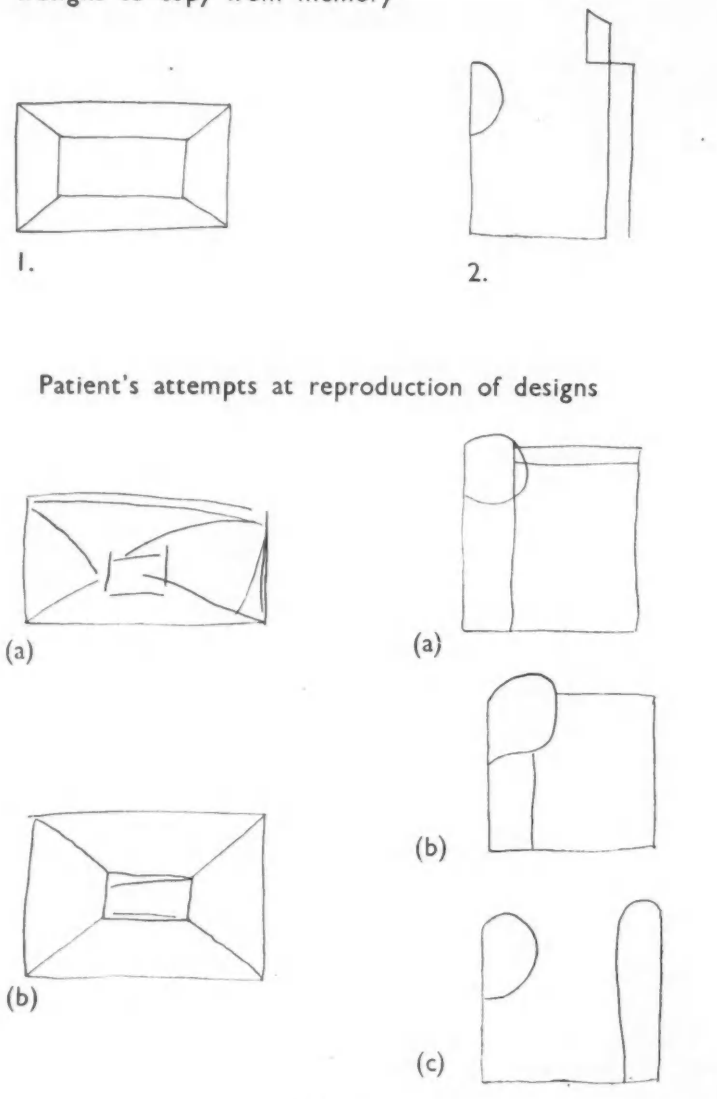

FIG. 5.

morning or afternoon, date, month and year. She was confused, however, regarding spatial orientation in maps, as shown by her drawing of the map of England. (**Fig. 6.**) She was correctly orientated regarding right and left.

She showed no visual disorientation, could divide a line into half and quarter, and recognized the nearest and farthest objects in two and three dimensions.

FIG. 6.

She could name her own fingers and those of her examiners correctly. She could name correctly all the parts of the body.

General knowledge.—The patient's general knowledge was very defective. It is possible that this was not evidence of a generalized intellectual deterioration, because the patient had been, in a sense, shut out of the world for some considerable time. Her particular universe must have been a strange and difficult one, giving her enough problems with which to cope, without taking account of passing events. She had at best a vague and inaccurate half-knowledge, compatible with her defects.

Q. Who is the Prime Minister ?
A. Atlee—Clement.
Q. Who is the King ?
A. George 7th.
Q. Whom did Princess Elizabeth marry ?
A. Milverd Haven, Prince Philip.

Stereognosis—The patient showed no astereognosis. Her eyes were covered and various objects put in her hand. She could name correctly keys, pencil, rubber, handkerchief, paper, comb, and could identify textures, e.g. rubber, linen, wool.

Memory of past events—The patient could give a good account of her past life, describing occupations, holidays, army experiences, with apparent accuracy, although she was somewhat confused regarding exact dates.

Praxis.—The patient could perform well in all those tests of praxis in which conceptual thinking was not required, e.g. in copying drawings of simple figures and making simple patterns with Koh's blocks.

The patient's failures show how necessary is adequate conceptual thinking for the performance of many of the tests of constructional praxis now to be described. Here again the patient's reliance on, and attachment to, the concrete can be clearly noticed.

In two dimensions—The patient could divide a line into equal parts, draw simple geometrical figures, and copy simple drawings. The patient gives a clear demonstration of her adherence to the concrete in the performance of one of the latter tasks (fig. 7). Apart from her performance in set tests, the patient often made spon-

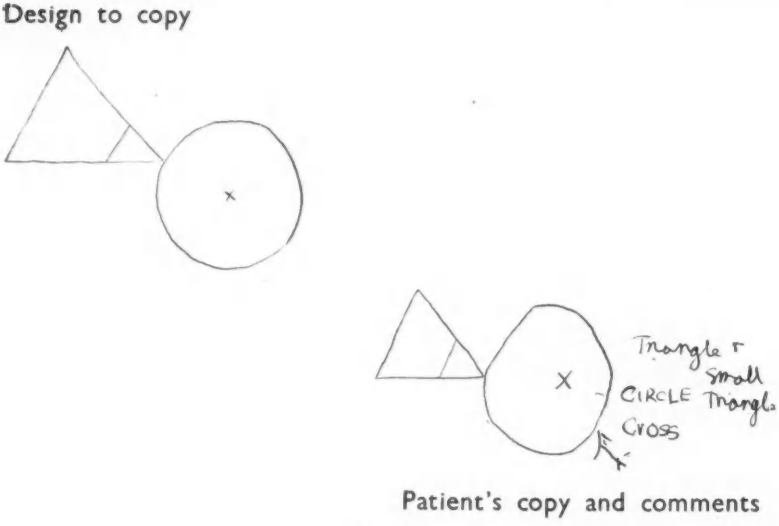

FIG. 7.

taneous sketches, of flowers, trees, houses, etc. These were generally copied from a book or from life.

In three dimensions—The patient could do embroidery, and could be taught some simple weaving and very simple toy-making. She was unable to do more than the first design with Koh's blocks.

Conceptual thinking.—The patient was unable to understand allegories, metaphors, parables or proverbs. This has already been discussed in connexion with the patient's reading. The patient was asked for lists of (1) animals, (2) flowers, (3) countries. She was able to give only those with which she had concrete associations. For example, the animals she named were all those contained in her glass menagerie. The countries were only those she had previously visited, or in which she had pen-friends. She was able to name only those occupations which she had herself undertaken, and only those rivers she had seen. When asked for a list of abstract nouns (following an attempt to explain the meaning of the term "abstract noun" and the examples of love and truth having been given) she wrote: "faith, renown, passage, rooms, light, dark, shadow." When asked for a list of flowers, the patient said: "Rose, red rose, dark red rose, pink rose, yellow rose, tea rose, cornflowers, dark blue and light blue . . ." The elaborate variation of the colour may be due to a desire to increase the list, the patient recognizing the poverty of her "flower category." It may also be due to a certain mental viscosity, the patient having difficulty in leaving one subject to go on to the next without a concrete connecting association. There were times when the patient was able to give a reasonably long list of various flowers, but it was then always possible to trace a thread of association with the concrete, for example: "carnation (father's favourite flower), lily of the valley (mother's favourite flower), rose (my favourite flower)." The patient herself spon-

taneously added the qualification. Or again, " daisies, cornflower, buttercup (flowers of the fields) " or when asked for a list of colours, " red, green, amber (traffic lights)." The patient was unable to make more than the first design with Koh's blocks. She was unable to grasp the principle of the game of noughts and crosses.

The above tests indicate a disorder of categorical thinking and a reliance on the concrete.

Auditory imagery and hallucinations.—The patient's auditory hallucinations are of interest. It has been stated (Seitz and Molholm, 1947) that schizophrenics with auditory hallucinations were found to have a significantly lower mean percentage of auditory imagery than normal subjects. The authors conclude that " not only do these findings disprove the old theory that auditory hallucinations are exaggerations of predominating auditory imagery, but they suggest the new concept, that one of the factors responsible for auditory hallucinations is relatively defective auditory imagery." The auditory imagery of our patient was found, on testing, to be grossly defective. She had, as stated above, been diagnosed as schizophrenic on account of her well-marked auditory hallucinations. Organic lesions in the auditory cortex are supposed to be present in this patient. The presence of visual hallucinations where the occipital cortex is damaged by organic lesions is well known, the most gross example occurring in Anton's syndrome. It is suggested that hallucinations of smell and taste, occurring as they do in " uncinate attacks," are present when some lesion is present in those areas of the cortex concerned with such senses. It would seem, then, that hallucinations are manifestations of a poverty, or lack of cortical function, in particular spheres.

The patient offered the information, on being directly questioned regarding auditory hallucinations, that she had heard voices, at the time of her admission to the mental hospital, " plenty of voices—soft and loud, day and night, a rattling of keys, a constant banging of doors." She also imagined the other patients were making derogatory remarks regarding her nationality—classing her, she said, as Italian, while in fact she was British.

Her mental imagery was tested in the following way : Various situations were mentioned to her and she was asked to give all associations—sound, sight, smell, or touch, connected with them. For example, she was asked for her associations with railway station, farmyard, seashore, a house on fire, crossing the street, going swimming. The patient was able to give a large number of associations but no single one of auditory nature was ever mentioned, as follows :

(1) *Railway station :* Liverpool Street Station, station master, porters, tea rooms, luggage room, trains coming in and out, bookstalls, booking offices, time tables.

(2) *Crossing the street :* Traffic lights, pedestrians, the Highway Code, posters.

(3) *A walk on the seashore :* The tide coming in and out, seashells, sand, seaweed, rocks, cliffs, blue sky, the Parade, gulls.

It is interesting to note that among the associations listed for " A walk in the woods," the patient wrote " Echo of footprints."

She was also asked to give the immediate association for a number of words, associated normally with sound, such as an air raid, bomb, rain, aeroplane. Some examples are given :

Air raid	" Shelter, damage caused."
Aeroplane	" Hangar, scattered aerodromes."
Rain	" Water and floods."
Bomb	" Atom, oil or gas."
Telephone	" Rush hour."

She was also asked for associations with words symbolizing noise, such as crash, splash, bang, knock, flap. Some examples are :

(1) *Crash :* " collision, knock, bruise."

(2) *Bang :* " might be thunder."

The patient was then asked to imitate noises made by various animals and birds, for example cuckoo, cow, cat. She was unable to do so although she could say the words "meaow, moo," as one who reads them aloud in a conversational voice.

The above tests indicate a relatively deficient auditory imagery in keeping with the auditory agnosia and auditory hallucinations.

Nature and localization of the lesions.—As regards the nature and localization of the patient's lesions, very little precise information can be offered. Many authors are of the opinion that there can be no well-defined localization of the functions concerned with the understanding and expression of speech. Hughlings Jackson (1864) believed that "speech could not be located in any small area of the brain—it must require a vast representation." Constantin von Monakow (1897) stated that "speech was located in the whole cortex." Henry Head (1920) was also of this opinion.

In many of the cases described in the literature of patients suffering from "word deafness," temporal lesions have been supposed, but seldom verified by post-mortem examination. Henschen (1920) described 3 cases of persisting word deafness, in which reading and writing were unaffected, and motor speech hardly affected. In two of these, bilateral temporal vascular lesions were found at post-mortem, in one, lesion of the right temporal lobe only.

As regards the nature of the lesion, nothing is known in our patient. It was considered that any investigation such as an encephalogram or arteriogram would have brought little benefit to the patient although it might have satisfied medical curiosity.

Discussion

Man can communicate with the outer world by means of his sensory system which is at the same time a barrier between the outer world and himself. We are surrounded by a universe of potential sensory stimuli which differ indefinably from one another and which may produce in us a meagre range of subjective sensations—hearing, seeing, tasting, smelling and feeling. A sensory stimulus may produce a subjective sensation at a single particular moment in time. The subjective sensation as it appears in consciousness (that is, as soon as the individual becomes aware of it) is already finely differentiated, not only according to a particular sense, but also within the sphere of that sense. We are aware of a particular sound, voice, or music, or machine, of a particular smell, or taste, or sight. We cannot be aware of undifferentiated sensation.

The differentiation of sensation depends upon and increases with experience of previous similar sensations. It seems that each sensation, as it occurs, has the ability to lay down an image of itself, which can b stored as a memory. While sensations can only occur at a given moment in time as the immediate result of a sensory stimulus, the recall of them may take place at any time. A further development may then occur. Sensations and their images may be endowed with symbolic representation. Each sphere of sensation has its peculiar range of symbols. Visual symbols take the form of designs—the figure and background of the Gestalt psychologists, of letters, words, mathematical figures, geometrical designs and colours.

Acoustic symbols take the form of words and musical notation. During the process of development, an individual comes to realize the relation

between a particular sensation and one previously experienced. After a number of such experiences, if the particular sensation or its image had been endowed with a symbolic representation, it is possible for the individual to abstract the symbol from the first sensation and transfer it to the second or third of its kind. Finally, he will be able to free the symbol entirely from its concrete situation. Here are the beginnings of abstract thought. The symbol exists as an isolated abstraction.

The relationship of sensations to one another is assumed in their symbolic representations which are not in themselves absolute but carry the qualities of similarity or difference which are essential for perception. There can be no light without dark, no sharp with blunt, no noise without quiet; blackness supposes whiteness, temperature is relative. Abstract thinking is thus dependent upon symbols. The more highly evolved the symbolic representation, the more abstract the thought processes. The theory of relativity was achieved not by sensory awareness alone, but by means of mathematical symbols.

Language consists of the symbolic representation of many forms of sensory experiences, and the symbols take the form of words and gestures. Language has a double function. It is used both for the expression of thought, and for the communication of thought from one individual to another. There exist, no doubt, sensory experiences for which the symbolic representations are inadequate, or absent, or not immediately available to an individual. These sensory experiences must be said to belong to language, being the source and inspiration of the symbols. In the study of the development of languages, the symbolic representation, or the naming of sensations, can be seen to occur, followed by the abstraction of the symbol.

It seems that lesions of the cortex may cause disturbances at various levels in the elements of language. The symbolic representations may be destroyed, in part or totally. The images may be destroyed, alone or together with the symbols. The subjective sensations may be affected, either alone or in any combination with the other elements. In this way there may be disturbance of expression or comprehension of spoken speech, gesture, or of written speech, or of both, or all the above together, or in selective combinations.

If the symbolic representations of expression of thought alone are destroyed, the result is the aphasic who "knows what he wants to say, but cannot find the word," an alert, frustrated individual, who may retain perfect awareness of his disability, and perfect comprehension of the spoken and written word. This is aphasia at the most superficial level. At a deeper level, the images may be destroyed, affecting the associations with previous learning. If, in this case, the symbols of expression are retained, jargon aphasia may occur. The patient makes use of a great store of symbols which are unconnected with previous images and in themselves meaningless. If acoustic images are destroyed, comprehension of the spoken word is generally affected. When images and symbols are

together destroyed, the quiet aphasic results. At the lowest level, there is a faulty or absent interpretation of the sensory stimulus. The patient described above belonged to this group. Her interpretation of auditory stimuli was affected. Symbolic representation was only partially affected.

A similar classification can be applied to the various types of alexia and agraphia, the disability depending upon the level of the defect—symbol, image, or subjective sensation.

Finally the purely motor components of speech must be considered—the dysarthria due to lesions of the motor and cerebellar systems, and of the tongue and larynx. Lesions of the optic and aural systems, causing blindness and deafness, also play a part in the disturbance of man's capacity for language, as does impairment of kinæsthetic sense.

While thought is dependent upon stimulus, sensation, image and symbol these are not the only factors influencing its performance. Individual qualities, " intelligence," age, sex, personality, imagination, together with circumstances and education, are important.

Language is also dependent upon these factors. Once the development of thought and language have begun, each relies upon the other for progression. Language assists thought ; thought is the source of language. The more complicated the thought, the greater is the need for language for its expression and comprehension by others. The more complicated the language, the greater the need for past experience in thought. Symbols are thus the means by which man attempts communion of himself with the mysterious outer world. They are the concrete expression of thought. They are the ladder to the other side of the moon.

Summary

A patient is described who suffered from a defective understanding of sounds including speech and music, although her hearing was not impaired. She had lost also the understanding of rhythm. Her auditory imagery was very defective. She was unable to think in terms of abstractions. Many symbols, such as those of arithmetic and grammar, were without meaning for her. She showed therefore a degree of acalculia. Her spelling was moderately defective, as was her grammar in written (but not in spoken) language. She was unable to perform two tasks simultaneously. She had, for a time, at the onset of her illness, suffered from auditory hallucinations. Expressive speech was very little disturbed. Reading was not impaired as regards the motor aspect, although comprehension of content, when dealing with abstract ideas, was defective. Writing was only slightly impaired—again not in the least as regards the motor aspect, but rather as regards punctuation, grammar and spelling. The patient showed no apraxia, no astereognosis, and no disorientation in space or time. She had little or no insight into her disabilities. She unconsciously used tactics of distraction to hide them. She preserved, in spite of them, a lively interest in current events, music, clothes, pen friends, embroidery, photography, reading and charitable works.

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SENSORY CHANGES IN PROCAINE NERVE BLOCK

BY

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INTRODUCTION

A REVERSIBLE dissociation of the various modalities of cutaneous sensation may be produced by the application of cold (Weber, 1847), pressure (Bastien and Vulpian, 1855), or local anæsthetics to a nerve trunk. Donaldson (1885) observed that cocaine instilled into the eye led to a dissociated anæsthesia, and in 1886 Goldscheider noted a similar phenomenon when cocaine was injected round the trunks of the median and ulnar nerves. Later, Bier (1899) studied the sensory dissociation produced in himself and others by spinal anæsthesia with cocaine. The general results of all these experiments have since been amply confirmed.

The question of the exact order in which the various sensory modalities are abolished assumed a new importance in 1929, when Gasser and Erlanger showed that the elevations in the electroneurogram of isolated frog and mammalian nerves exposed to the action of cocaine disappeared in a characteristic order. They attempted to deduce, from a study of the literature on sensory dissociation by local anæsthesia, which modalities of sensation were carried in fibres of a given diameter group. This proved to be difficult, since the published work contained a number of contradictions. These contradictions led Heinbecker, Bishop and O'Leary (1932, 1934) to carry out sensory tests during both spinal and peripheral blocks, and to compare their results with a repetition of Gasser and Erlanger's experiment, in which procaine and not cocaine was used. Some of their results conflict with those of previous workers, and the present investigation was undertaken in order to examine the reasons for these discrepancies. This paper deals with the manner in which the various modalities of sensation disappear and return when a nerve trunk is blocked with procaine.

TECHNIQUE

(1) *Anæsthetic.*—The subjects used were all healthy young male adults, the majority being medical students. In 20 men one or other ulnar nerve, usually the left, was blocked; 4 of these had the experiment repeated some weeks later. In another 5 subjects one or other lateral popliteal nerve was used. A total of 29 blocks in 25 subjects was thus observed.

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The anæsthetic used was procaine hydrochloride in strengths varying between 1½ per cent and 2½ per cent, with or without adrenaline. Initially a 1 : 200,000 solution of adrenaline was used, but it was found that this tended to produce an unnecessarily prolonged period of complete anæsthesia. In a few experiments the adrenaline was therefore omitted altogether, but the period of anæsthesia was now occasionally uncomfortably short for experimental purposes, so that a compromise was reached whereby 1 : 800,000 adrenaline was employed.

The ulnar nerve was blocked in the ulnar groove at the back of the elbow and the lateral popliteal nerve at the neck of the fibula. The solution was infiltrated round, but not into, the nerve trunk, since a gradual onset of sensory paralysis was necessary for accurate observations. The quantity used varied widely in different subjects, but was kept as small as possible. For this very reason, however, it was occasionally necessary to make a second injection if the first proved inadequate to produce anæsthesia. The mean figure for the total amount injected was 10·9 c.c. in the ulnar group and 11·6 c.c. for the lateral popliteal blocks.

(2) *Sensory testing.*—In the ulnar blocks the procedure adopted was very similar to that described by Sinclair (1948) for the investigation of pressure blocks of the ulnar nerve. On the palmar surface of the hand six circles 1 cm. in diameter were stamped out with marking ink in the line of the fifth digit, and numbered 1 to 6 as shown in fig. 1. Sensory stimuli were applied to these circles at intervals, the order in which the circles were tested by any given stimulus being randomized. A stop-watch was used to time the experiment.

For eliciting the sensation of touch, a piece of No. 2 nylon suture material 2·5 cm. long, mounted on a 25 cm. metal rod, was employed. The nylon thread had a diameter of 0·17 mm. and was capable of holding down a weight of 500 mg. It was used vertically, so as to deliver a punctate stimulus to the skin. In any given circle, these stimuli were applied at random to the area of skin enclosed by the circle. The subject was instructed to keep his eyes shut and to reply as soon as he felt himself touched.

Pain sensibility was tested by means of a round-bodied needle 12·5 cm. in length. The pricks were given by hand, and an attempt was made in all cases to deliver a uniform vertical prick which just failed to draw blood.

Temperature sensibility was tested by allowing a glass test tube, 1·5 cm. in diameter, half-filled with water, to rest by its own weight on the area to be tested. A thermometer in the tube was read before and after each test. The temperature of the cold stimulus was 15° C., and that of the warm stimulus 45° C.; neither figure is exact, but the actual temperatures did not depart from them by more than plus or minus 2 degrees; it was felt that the advantage of simplicity outweighed the disadvantage of inaccuracies of this order. Neither stimulus caused any pain when applied to the normal skin of the ulnar area. In all temperature tests

precautions were taken to prevent the subject guessing the nature of the stimulus from factors other than the sensation experienced.

The subject was familiarized with the stimuli before the block was begun, and his capacity to appreciate all the stimuli in all the testing areas was checked. When the block was at its height another check was made to ensure that all the testing areas lay well within the autonomous zone of the ulnar nerve. This was done by roughly mapping out the areas of sensory loss to touch and pain. The boundary of pain sensibility was delimited by pin-prick, and that of touch by stroking stimuli from a No. 4 nylon thread.

In the lateral popliteal blocks only three testing areas were used (fig. 2), but the procedure was otherwise exactly the same. Since the chance of one of the marked testing areas lying outside the autonomous zone was in this case rather greater, each area was duplicated by an alternative one at the same level but to one or other side. At first all six areas were tested, but as soon as it became clear which areas lay within the autonomous zone, one out of each pair was deleted, leaving three areas only. At the preliminary testing, it was occasionally found that the touch or temperature stimuli were inadequate to arouse sensation in one or more areas ; in such cases a stimulus of greater intensity was substituted (a No. 3 nylon thread for touch, and hotter or colder water in the temperature tube).

Since skin touch and hair touch behave differently in pressure blocks (Sinclair, 1948) the hair of the leg in the region required for testing was clipped short (not shaved), and care was taken to deliver the touch stimuli to the skin without stimulating the remaining stumps of the hairs.

Results

Manner of sensory failure.—Sinclair (1948) has described the gradual and progressive manner in which the modality of touch becomes extinguished in asphyxial blocks of the ulnar nerve. This description also applies closely to the way in which touch sensibility disappears in a procaine block. Within a given testing circle misses appear at random, and the response caused by stimuli which are still effective is often either altered in quality or prolonged for several seconds, the subject complaining that the thread is not being applied vertically, but is stroking or tickling a fairly wide area surrounding the actual point of stimulation. A distinct delay also appears between the application of the stimulus and its perception. At this stage a stimulus applied to the testing circle at random may produce either no response, a delayed response, a delayed response altered in quality, a prompt response altered in quality, or a response indistinguishable from normal. The number of altered responses increases, as does the number of misses, and eventually " anæsthesia " supervenes. Now, however, a stronger stimulus will still produce a response ; thus a No. 3 nylon thread may still give 100 per cent responses several minutes after no response can be elicited by a No. 2

nylon thread. When this in turn fails a No. 4 thread may still be effective, and so on. It is therefore evident that for comparative purposes some sort of end-point in this continuous and progressive process must be defined. For the present investigation this end-point was defined as the stage at which at least 50 per cent of stimuli delivered with a No. 2 nylon thread at random within the area were not appreciated, the number of stimuli used for determining this figure being either six or eight.

The changes in the response to a pin-prick in a procaine block are similar to those described for pressure blocks by Weddell, Sinclair and Feindel (1948). Alteration in the quality of the response precedes a prolongation of the sensation, followed by a delay in its perception, increasing numbers of failures to respond, and finally complete analgesia. A prick drawing blood can be perceived several minutes later than a prick that does not, and pain caused by pinching the skin with epilation forceps persists longer still. The definition of an end-point for pain is more complicated than the definition of one for touch. As the block develops, the sensation aroused by a pin-prick, at first compounded of a sharp prick plus pain, becomes altered in quality, and then reaches a stage where the sensation is one of sharpness only ; later this in turn disappears, so that the subject can no longer distinguish the point of the needle from the end of a blunt rod, both stimuli being reported as " pressure." Obviously to take as the end-point the stage at which 50 per cent of these remaining pressure responses are abolished would give no idea of the behaviour of pain sensibility ; the end-point must thus be qualitative as well as quantitative. The stage chosen was that at which 50 per cent or more of six pin-pricks delivered at random within the test circle are no longer appreciated *as painful*. This definition necessitates a subjective distinction between " sharp and painful " and " sharp " which is sometimes exceedingly difficult to make ; nevertheless, this appears to be the only practicable stage to select.

The disappearance of temperature sensibility follows a similar pattern. Quality changes may occur, as in pain and touch, but are not so common as paradoxical sensations, hot being reported as cold and vice versa.[1]

The delay in perception is longer than for pain, and much longer than for touch. An increase in the temperature of the warm stimulus prolongs the time during which warmth will be reported correctly, and a decrease in the temperature of the cold stimulus acts similarly for cold. Owing to the persistence of the pressure component of the stimulus complex, the end-points for temperature sensations must be qualitative in the same way as that for pain. For warm stimuli the end-point taken was that at which 50 per cent or more of six applications are no longer recognized *as warm*, and the end-point for cold was similarly defined as the stage when 50 per cent or more of six stimuli are no longer felt *as cold*.

[1] Paradoxical warmth (Pavlicek and Jenkins, 1933) was, in these experiments, rather more frequent than the more commonly discussed paradoxical cold (Alrutz, 1897).

Sensory dissociation in ulnar area.—In 6 subjects the order in which the various sensory modalities disappeared was recorded, using the standard stimuli and end-points defined above. Three ulnar testing areas were used—numbers 1, 4 and 6 in fig. 1—and for each area the four modalities were given a ranking score on the basis of the order of their disappearance, the first to go being ranked as 1, and the last as 4. Whenever the times recorded showed a difference of two minutes or less between the failure of two modalities, these were ranked as equal, and the available ranking score divided between them; thus a tie for second place between warm and pain would result in each being given a rank of $2\frac{1}{2}$. This was done since the testing of any modality in all three areas might take up to two minutes, particularly in the case of temperature; it was therefore felt that a difference of less than this time might often be without significance. The results of individual experiments in a given area were then added together, a procedure which Kendall (1945*a*) has shown to give the best estimate of the true rank. The results of this procedure are given in Table I, and show that the overall order of loss in the ulnar area was pain first, followed by cold, warm and touch in that order. The data from which this result is derived have a coefficient of concordance (Kendall, 1945*a*)

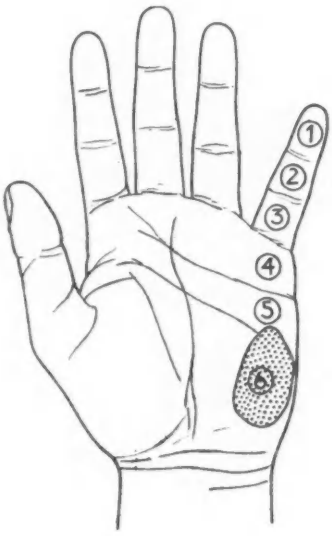

FIG. 1.

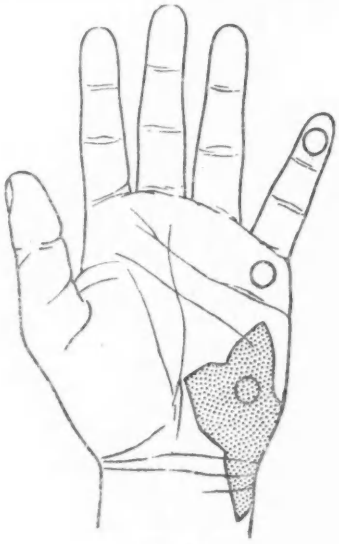

FIG. 2.

FIG. 1.—Position of numbered testing circles in ulnar area. The shading represents the area of touch loss in a subject in whom complete loss of sensation occurred in the palmar portion of the ulnar area at a time when sensation in the digital portion was unaffected (*see* text).

FIG. 2.—Position of numbered testing circles in lateral popliteal area.

which is just over the 5 per cent level of statistical significance ; they are therefore homogeneous enough for the total rank to have some meaning.

Effect of site of stimulation.—Nevertheless, the coefficients of concordance for each area considered separately are far from significant, and, for example, there is nothing to choose between touch and warm in areas 4 and 6, the lower rank of touch in the total being entirely due to the fact that it usually persisted longer than warm in area 1. Similarly, pain was ranked lower than cold in area 1, but higher in areas 4 and 6. In other words, it appears that the site of stimulation can affect the order in which the sensory modalities are lost. That this effect may on occasion be gross was shown by an examination of the individual results. Thus, in one man Cold disappeared *first* in areas 1 and 4, but *last* in area 6. In another, Touch failed last in area 1, but ranked second in both the other areas.

The ranking of all possible pairs of sensory modalities were subjected to closer statistical analysis, any tied rankings being distributed equally between the members of each pair. Thus, pain failed *with* touch in 2/18 areas tested, and *before* it in 16/18 areas. These figures were treated as though pain had failed *after* touch in 1/18 areas and *before* it in 17/18. This result differs significantly from what would be expected on a pure chance hypothesis ($p<0{\cdot}01$), so that it may be said that in these experiments pain failed significantly more often before touch than after it. Similarly, pain tended to disappear before warmth ($p < 0{\cdot}05$). No statistically significant relationship was found between any other pair of modalities.

In an additional three men a peculiar type of anæsthesia occurred. During the development of the block there appeared on the hypothenar eminence an area of apparently complete loss of all sensory modalities ; by using touch and pain stimuli sharply defined and reproducible borders to the area could be demarcated. The area was more flushed than the rest of the ulnar territory, and its skin temperature was higher ; outside its borders sensation was for a considerable time almost unimpaired, though it became partially affected later. Within the affected area in two of the subjects touch sensibility disappeared some time before pain sensibility, i.e. a direct reversal of the usual average order of loss. The areas affected in two of these men are shown in figs. 1 and 3, which show only the margin of touch loss : the areas in which pain sensation was completely absent were almost exactly the same.

Reproducibility of results.—In two of the subjects exhibiting this anomalous sensory paralysis a second block of the same nerve was done some weeks later. In both, a paralysis of the whole ulnar area gradually developed in the usual fashion. The distribution of the sensory paralysis was thus both spatially and temporally different. For example, in area 6 of one subject the order of loss on the first occasion, when he had a circumscribed area of complete paralysis, was cold, touch and warm together, followed later by pain. On the second occasion, when a more typical block developed, the order of loss in this area was pain, warm,

touch, cold. In area 1 of this subject the order of loss was similar in both experiments, and in area 4 no comparison could be made, since in the first block cold was the only modality to be lost in this area.

In addition, two more subjects whose initial block was of more or less standard pattern underwent a second block of the same nerve. In both cases the results of the second block were in substantial agreement with those of the first, any differences observed being in minor points of detail. The conclusion drawn must therefore be that, while a second block on the same subject may give a very similar result, it can on occasion lead to a grossly different one.

Effect of variation in normal sensibility.—One subject could not, at the preliminary testing, appreciate the 45° C. stimulus as warm on area 1, though he could readily feel it on areas 4 and 6. Several others, in whom all six areas were investigated, stated that temperature stimuli were much less readily appreciated on the finger (areas 1, 2 and 3) than on the palm (areas 4, 5 and 6); rough testing on a number of other subjects indicates that this is a fairly general finding. In all the instances where temperature sensibility was initially poor, it appeared to be lost early relative to the other modalities, whereas in areas where temperature stimuli were initially easily appreciated it appeared to persist for longer. These results suggested that some at least of the differences in the order of sensory loss might be explicable on the basis of differences in the normal sensibility of the skin in the three areas tested. It was thought that this suggestion might be supported if, in an area in which touch sensitivity was initially of a low order relative to that of the other modalities, the place of touch in the average order of loss was found to be different. Since no such area exists in the hand, attention was turned to the leg.

Sensory dissociation in the lateral popliteal area.—The lateral popliteal nerve was blocked in 5 subjects; in one of these the distribution of the nerve was anomalous, and many of the results had to be discarded. The information on sensory dissociation obtained from the other four is shown in Table II. When the total apparent ranking (touch, pain, cold, warm) is tested statistically (Kendall, 1945*a*) the data are found to be not significantly concordant, so that little weight can be attached to it.

As in the ulnar territory, there are discrepancies between the three areas tested; thus there are considerable ranking differences between touch and warm in areas 1 and 3, but none in area 2. In one instance an exact reversal of the average ulnar order of loss was recorded (touch, warm, cold and pain in that order), and in another temperature sensibility persisted apparently unimpaired throughout, though both touch and pain failed over a wide area round the testing circle.

The ranking of individual pairs of modalities was investigated as in the case of the ulnar blocks, but in no instance did any one modality fail significantly more often before another than after. The most suggestive comparison was that of pain and touch: pain failed *with* touch in 9/12 areas, and *after* it in 3/12 areas. When the figures for any given pair of

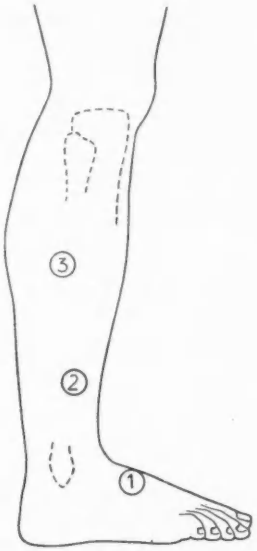

FIG. 3.—The three ulnar areas selected for comparison by the use of standard stimuli. The shading represents the area of touch loss in another subject (cf. fig. 1) in whom complete anæsthesia occurred in the palmar territory before the digital territory became affected (*see* text).

modalities in the lateral popliteal area were compared with the figures for the same pair in the ulnar area in a 2 × 2 contingency table, a significant difference was found between the two nerve territories in respect of the relationship of pain and touch ($p < 0{\cdot}01$). No other significant differences between the ulnar and lateral popliteal blocks were found. In the ulnar area touch was usually the last modality to fail, while in the lateral popliteal experiments it was usually the first, the same stimuli and end-points being used on both occasions.

When the data for the ulnar and lateral popliteal blocks were pooled, the ranking of sensory loss was pain, cold, touch, warm, and the coefficient of concordance of this rank now fell far short of significance. Since this coefficient was just significant for the ulnar data considered alone, this finding may be taken as additional evidence of a discrepancy between the ulnar and lateral popliteal results. In the pooled data, the only statistically significant finding was a tendency for pain to be lost before warm ($p < 0{\cdot}01$).

Owing to minor variations in the cutaneous distribution of the lateral popliteal nerve, on a few occasions one of the pairs of testing areas was found to be located in a zone of overlap from a neighbouring nerve. On one such occasion it was observed that all modalities except that of pain failed in the circle tested; in the adjacent circle, which lay inside the autonomous zone, pain was the first modality to disappear.

In the lateral popliteal blocks an observation made on the back of the hand was confirmed ; the sensation of touch aroused by stimulating hairs persisted considerably longer—often as much as ten minutes—than that aroused by stimulating the skin. Indeed, in one area the loss of skin touch preceded the loss of pain by four minutes, while hair touch in the same area did not disappear until seven minutes *after* the loss of pain. It was also observed incidentally that in the lateral popliteal distribution the margins of the area of loss of skin touch lay well outside those of the area of loss of hair touch.

Mode of spread of anæsthesia.—In the modality of Touch there was a tendency for the three ulnar areas tested to fail in the order 6, 4, 1 ; this is the general order of increasing sensitivity to touch, but could also be represented as a proximo-distal spread of anæsthesia. Similarly in the lateral popliteal blocks, it was found that area 1, the most distal, retained touch sensibility longer than the others. In view of the findings of Endres (1929) who described a proximo-distal spread of anæsthesia in the territory of a cutaneous nerve in the thigh, and of the comments of Lewis and Pochin (1937), who confirmed his work, it was thought desirable to try to establish whether or not the progressive anæsthesia under consideration was centrifugal in nature ; that is, if in any one modality the most proximal area tested tended to fail first, followed by the next most proximal, and so on.

A return was made to the ulnar area, and the order in which a given modality failed in each of the six testing circles was investigated in a number of subjects. Owing to the lack of time imposed by the steady advance of anæsthesia it was rarely found possible to test all four modalities fully in all six areas, so that as a rule full information on two or three modalities only was obtained in any one subject. Table III shows the results of applying to these subjects a ranking procedure exactly similar to that described for the evaluation of the sensory loss in a given area. The ranks for each modality in each area were totalled, and then arranged in order. The figures in Table III therefore show the *average* order in which each modality disappeared from the six areas listed. In no modality does there appear to be any suggestion of a centrifugal spread of sensory paralysis, nor is there apparently much correspondence between the spatial dissociation of one modality and that of another. For example area 3 is, on the average, the first area in which touch becomes lost, but is almost the last in which cold sensibility persists. For none of the rankings is the coefficient of concordance statistically significant, so there is no indication that they are due to causes other than chance.

In order to test statistically the hypothesis of a regular proximo-distal spread of anæsthesia the rank obtained in each individual experiment was correlated with the hypothetical rank in which area 6 failed first, followed by areas 5, 4, 3, 2 and 1 in turn (Kendall, 1946). In view of the existence of ties in the data, the rank correlation coefficient was calculated by the method of Woodbury (Woodbury, 1940; Kendall, 1945*b*).

This coefficient was positive, indicating a degree of correlation, in 16/26 rankings; in the remaining 10 it was zero or negative. Only two statistically significant values were obtained, one in the touch data which indicated a proximo-distal spread ($p<0{\cdot}01$), and another in the warmth data, which, being negative, indicated a disto-proximal spread ($p<0{\cdot}02$).

In the four lateral popliteal blocks already described the order in which the areas failed in any given modality is shown in Table IV. Though it is difficult to make any deductions when only three areas are used, these results also indicate no regular proximo-distal trend. In short, the results support Endres' finding of a spatial as well as a temporal dissociation of sensibility, but suggest that it is not possible to generalize his observation that this follows a centrifugal pattern.

Recovery of sensation.—The recovery of sensation was usually a more leisurely process than its disappearance, in the sense that the interval between the disappearance of two modalities in a given area might be three or four minutes, whereas the interval between their reappearance might be as much as twenty minutes. The criteria used to time sensory " recovery " were similar to those used for sensory " loss "; thus touch sensibility was considered to have recovered when 50 per cent or more of six stimuli were appreciated within the area tested, and so on. In both the ulnar and the lateral popliteal blocks the order of sensory recovery was in general the reverse, or almost the reverse, of the order of sensory loss, the sensation which became paralysed last being paralysed for the shortest time. There were, however, exceptions. For example, in area 6 of one ulnar block, sensation was lost in the order pain, warm, touch, cold, and subsequently recovered in the order warm, touch, cold, pain. The overall ranking order of sensory recovery was touch, warm, cold, pain, but the coefficient of concordance of this rank was not statistically significant.

On one occasion a complete motor and sensory paralysis of the ulnar nerve developed within two and a half minutes of the termination of the injection—so fast that no distinction was possible between the time of loss of the various modalities. It was thought that this resulted from the injection being made in error into the ulnar nerve itself, instead of alongside it. In this man it was found that the four modalities recovered in the usual fashion one after the other, the interval between the recovery of touch (which was the first to return) and that of pain (which was the last) being some sixty minutes.

Effects of Modifying Stimuli

Alteration of intensity.—It has already been noted that in any modality an increase in the intensity of the stimulus may lead to a delay in the appearance of the end-point. The effect of this on the apparent order of loss of sensation may perhaps be illustrated by an example. In areas 1 and 3 of an ulnar block experiment a stimulus of 38° C. was consistently reported as " cold " five minutes after the injection was completed ;

a stimulus of 42° C. continued to be appreciated as "warm" for an additional fifteen minutes. Now in these areas the end-point for pain was recorded at ten minutes. Hence, if a temperature of 38° C. had been reported as standard, warmth would have been recorded as failing *before* pain, while if 42° C. had been the standard, warmth would have been taken to fail considerably *after* pain. Similar examples in other modalities could be multiplied, and by a judicious manipulation of the stimulus intensities used it was found possible to record almost any desired order of sensory loss. Similarly, the order of return of sensibility could be grossly influenced by the intensity of the different stimuli used.

Alteration of size.—In the modalities of touch and pain, when stimulation of one small area of skin fails to elicit a response, stimulation of another a millimetre or so away may still do so. Hence if the stimulating surface could be made larger, in theory the responses would persist longer. No attempt was made to demonstrate this with either touch or pain, but a similar effect may readily be observed with temperature stimuli. If the area of contact is increased by pressing the side of the tube against the hand, the stimulus continues to be perceived considerably longer. The end-point may be postponed further by rolling the tube over a small area instead of allowing it to remain at rest, and still further if the area to be tested is immersed in water at the same temperature as that in the tube.

Alteration in duration.—The characteristic delay which occurs between the application of the stimulus and the perception of the response at a certain stage of failing sensibility has already been referred to, and is particularly evident in the case of temperature stimuli. If a warm tube is applied it may take perhaps five seconds before the stimulus is recognized as warm, and if the tube is removed before this, the result may be recorded as "indifferent." If paradoxical sensations are produced, they may precede the recognition of the true nature of the stimulus. Thus a warm tube may first be reported as "indifferent," then as "cold," and only after seven or eight seconds recognized as warm. This final verdict will not be altered if the tube is maintained in position for another ten seconds. Though this sequence does not occur in every case, it is necessary to leave all temperature stimuli which are initially reported wrongly in position on the testing area for at least ten seconds. If this is not done, a false result may be recorded, so altering the relation of the temperature end-point to that of other modalities.

Repetition of temperature stimuli.—It was frequently observed in this series that a cold stimulus which elicits an erroneous response at the first application will be recognized later if testing is continued. An example may be given from a lateral popliteal block in which cold stimuli were applied to the skin in the same spot for periods of five seconds, the interval between applications being also five seconds. Three runs of six applications each gave the following responses: at 59 minutes, "hot, hot, indifferent, hot, cold, cold"; at 67 minutes, "hot, hot, hot, cold plus

pain, cold plus pain, cold "; at 72 minutes, " hot, hot, cold plus pain, cold plus pain, cold, cold plus pain." This phenomenon has not yet been fully investigated, but it appears to be associated with the cooling down of the area of skin by repeated application of the cold tube. It may be noted in passing that the skin of the area tested is raised in temperature by the vasomotor paralysis induced by the block, and this factor must always be taken into account in evaluating the responses to temperature stimuli in procaine block experiments.

A similar effect was observed in the modality of warm : in a number of instances a warm stimulus was at first reported as " cold," but on repeated application eventually became recognized correctly.

Alternation of stimuli.—If the warm and the cold stimulus were applied alternately to the same area of skin, the subject could often distinguish between the two at a time when he was unwilling to hazard a guess at the identity of either when applied singly. In several subjects this faculty of distinguishing by contrast persisted long after either stimulus had ceased to produce a response having any apparent temperature content. No subject could explain how this differentiation was done ; the stimuli simply " felt different." Similarly, after the failure of pain sensibility the subject could often distinguish the point of the needle from a blunt rod if the two were applied alternately to the same area, while he would be at loss to identify them when applied separately.

Discussion

The results of previous investigations dealing with the order of sensory loss in chemically induced anæsthesia are perhaps most clearly appreciated in tabular form. Table V summarizes briefly the information obtained from regional nerve blocks, while Tables VI and VII give data for spinal and local anæsthesia respectively. Some of the observations were made incidentally in the course of another investigation, and in others the data given are fragmentary. At first sight there appear to be great discrepancies between the results reported by different workers. Nevertheless, a closer examination shows that it is invariably reported that pain sensibility is lost before that of touch, which is always the last to fail. The very considerable divergence of opinion which appears, both within any given table and between one table and another, is exclusively concerned with the relationships between pain and temperature sensibility. The reason for these disagreements has been shown by the present investigation to lie in the existence of a large number of complicating factors which are capable of totally destroying the value of any statement on the order of sensory loss, unless so hedged about with qualifications that it becomes useless for comparative purposes. Some of these factors have previously been recognized, but the possible magnitude of their influence has been under-estimated, while others do not appear to have been seriously considered.

In 1907 Trotter and Davies recognized the desirability of defining

degrees of anæsthesia : " When we bear in mind how common is relative anæsthesia, and how it includes all stages of loss from the just not normal to the almost complete tactile anæsthesia, we cannot but realize that there must be distinguishable steps in this wide range . . ." In a gradually progressive anæsthesia such as occurs in procaine block these "distinguishable steps " can be mapped out by the failure of the area tested to respond to progressively stronger stimuli (cf. Grundig, 1930 ; Zottermann, 1933). This fact was recognized by Heinbecker, Bishop and O'Leary (1934) who observed that " when the sensation of warmth is abolished and pain is felt, a stronger stimulus for pain is required than normal, because by this time some pain fibres will have been blocked . . ." They did not, however, observe that by adjusting the stimuli not only could pain be made to disappear before warmth but even touch before pain. In short, it is meaningless to say that pain disappears before touch unless what is meant by both " pain " and " touch " is rigidly defined. This point was emphasized by Cobb (1919) who found that in peripheral nerve lesions the area of analgesia could be made larger or smaller than the area of anæsthesia to touch merely by varying the weight on the testing needle. He concludes : " Dissociations of sensation due to peripheral nerve lesions arise from comparing stimuli not only qualitatively different but quantitatively unequivalent. In short, they are artefacts . . . For clinical sensory examination quantitatively standardized stimuli should be used." Even standard stimuli will not, however, give reproducible results if they are not used in a standard manner. Thus, a nylon thread will give a very different result according to whether it delivers a vertical punctate stimulus or a horizontal stroke. It is probable that much of the confusion as to the order of sensory loss in chemical anæsthesia is due to the fact that no two workers appear to have used exactly the same set of stimuli ; indeed, in the majority of the papers the methods of sensory testing and the end-points adopted are not described.

The difficulty of defining a reproducible end-point in any modality is due partly to the manner in which each modality fails, and partly to the impracticability of delivering a pure stimulus, i.e. one that will stimulate one modality only. Thus, any form of painful stimulus will also involve stimulation of either warmth, cold, touch or pressure endings, and the resultant sensation is a mixed one, so that the time of the withdrawal from this complicated experience of, say, the pain element is a point very difficult to define subjectively. Heinbecker, Bishop and O'Leary note this difficulty, and point out that alterations in the quality of sensibility, if present, may render the masking of one sensation by another still more troublesome. Little attention, however, appears to have been paid in previous work to the problem of defining satisfactory end-points, and in a number of instances the subjects used have been hospital patients with (presumably) no experience of psycho-physiological work.

Gross differences in the order of sensory loss may be found between one

part and another of the distribution of the blocked nerve and also between the territory of one nerve and another. Some of these differences may be due to variations in the normal sensibility to the four modalities of sensation in different parts of the body. The discrepancies are often as great or greater than those which have been reported between regional blocks and spinal blocks, and it is interesting that these regional blocks have usually involved the nerves of the upper limb, while the spinal blocks must, by their nature, have been tested mainly on the lower limb. The early disappearance of touch in the present series of lateral popliteal blocks is in contrast to the reports of its late persistence in spinal blocks (*see* Table VI). This difference may be due to several factors, as for example the employment of relatively gross touch stimuli, the stimulation of hairs, or testing in a region more sensitive to touch stimuli than the territory of the lateral popliteal nerve.

The degree of variation between subjects does not seem to have been realized, and many reports appear to be based on the study of too few subjects. Again, some workers (Heinbecker, Bishop and O'Leary, 1934) appear to rely on the order in which the modalities of sensation return; this is not, however, always the reverse of the order in which they are lost, and affords no more consistent information than the order of sensory loss.

In short so numerous are the factors which effect the result in a given experiment that any desired order of sensory loss can be achieved by selection of either testing site or stimulus, or both.[1] While the results obtained in the present investigation are strictly speaking applicable only to procaine nerve blocks, it appears likely that similar effects might be demonstrable in the course of experiments on sensory dissociation induced by other means, such as the application of pressure or of cold. Indeed, Lewis and Pochin (1938) have already shown that in asphyxial blocks of the upper limb there is great difficulty in deciding the order in which sensation is lost because each modality is lost in a steadily progressive manner. They point out that the time of disappearance of a given modality can be influenced by alterations in the intensity and in the size of the stimulus, and though they give a definite order of sensory loss they do so with considerable reservations.

Two further points must be considered. Endres (1929) found that the anæsthesia produced by blocking with novocain a cutaneous nerve of the thigh spread proximo-distally, and concluded that this was due to the fibres destined for nearby points lying most superficially in the nerve as it emerged from the deep fascia, while those going more distally lay axially; the solution could only reach these central fibres after affecting the superficial ones. In 1937, Lewis and Pochin, using cutaneous

[1]There are theoretically 75 different orders in which the 4 modalities may be placed. The number of different orders recorded in this investigation has not been calculated, but in the 18 testing areas of the six ulnar blocks in which standard stimuli only were used, 15 different orders were observed.

nerves of the forearm, confirmed Endres' results and placed upon them the interpretation that fibres in the nerve running to distal points were intrinsically different from fibres running to more proximal points—a theory first advanced by Lewis, Pickering and Rothschild (1931) to account for what they assumed to be a disto-proximal spread of anæsthesia in human limbs, during compression. Sinclair (1948) has recently shown that, with respect to compression blocks, there is no necessity to postulate such a hypothesis. Further, no regular " centrifugal " anæsthesia occurs when the ulnar or the lateral popliteal nerve is blocked with procaine. Cursory examination indeed suggests a proximo-distal spread, but closer investigation shows that the anæsthesia spreads irregularly throughout the area tested. It may well be that the chief factor determining where, say, tactile anæsthesia will first appear is the initial sensibility of different parts of the territory of the nerve to touch, but this has not as yet been proved.

In two of the ulnar blocks in this series a spatial dissociation of anæsthesia of a rather different kind took place, such that during the development of the block an area of total or almost total anæsthesia could be mapped out on the proximal part of the hypothenar eminence, while the distal and dorsal parts of the ulnar area retained almost normal sensibility. It is difficult to explain such occurrences except on the basis that the fibres supplying the area affected were segregated in some way from the others. The ulnar nerve at the elbow occasionally consists of a single large fasciculus, with one or two small separate bundles running within the same outer sheath (Sunderland, 1949), and it is tempting to suggest that in these men one such small bundle might have contained a fasciculus supplying the hypothenar eminence. If so, the anæsthetic, penetrating from the outside, might have affected it first, before penetrating into the main nerve bundle; when the experiment was repeated, the anæsthetic may have penetrated from another angle or at another level, and affected the whole of the nerve almost simultaneously.

Summary and Conclusions

The manner in which sensation is lost during the development of procaine blocks of the ulnar and lateral popliteal nerves has been investigated in 25 subjects, and a number of incidental observations on sensory phenomena encountered during this process have been made. It is rather generally assumed that the order of sensory loss in procaine nerve block follows, with minor variations, a relatively stereotyped pattern, pain being the first sensation to disappear, and touch the last. However, the evaluation of the results in a given sensory dissociation experiment is a more complex task than has generally been supposed, since they depend on a multiplicity of factors, some of which may exercise an effect even more decisive than the manner in which procaine attacks the sensory nerve fibres. The chief of such factors are the nature and manner of application of the sensory stimulus and the region of the body to which it is applied. It is indeed impossible to generalize as to the order of sensory loss from

the results of even a large number of experiments, since by suitable adjustment of the experimental conditions almost any desired order of sensory loss may be recorded. There is no evidence to suggest that the paralysis of any modality takes place in a centrifugal way within the territory of the nerve affected, and it is probable that differences in the initial sensitivity of the skin in different parts of this territory may be responsible for the mode of spread of anæsthesia. The difficulties encountered in the subjective side of experiments of this nature make it essential to use either trained observers or intelligent volunteers with at least some scientific background.

TABLE I.—TEMPORAL SENSORY DISSOCIATION IN ULNAR AREAS

Site of stimulation	*Pain*	*Cold*	*Warm*	*Touch*
Area 1	12½	10	14	23½
Area 4	9½	12	19½	19
Area 6	8½	15	18	18½
Total	30½	37	51½	61

The figures are the sum of the individual ranks allotted to each modality as described in the text.

TABLE II.—TEMPORAL SENSORY DISSOCIATION IN LATERAL POPLITEAL AREAS

Site of stimulation	*Pain*	*Cold*	*Warm*	*Touch*
Area 1	9	10	14	7
Area 2	12	9½	9	9½
Area 3	9	11½	12½	7
Total	30	31	35½	23½

The figures are the sum of the individual ranks allotted to each modality as described in the text.

TABLE III.—SPATIAL SENSORY DISSOCIATION IN ULNAR AREAS

Modality	*No. of subjects*	*Testing areas* 1	2	3	4	5	6
Touch	6	6	4	1	5	2	3
Warm	4	2	1	3	4	6	5
Cold	7	2	4	5	6	3	1
Pain	9	6	4	1=5		1=3	

Average rankings showing order of failure of numbered testing areas.

TABLE IV.—SPATIAL SENSORY DISSOCIATION IN LATERAL POPLITEAL AREAS

Modality	*No. of subjects*	*Testing areas* 1	2	3
Touch	4	1	2	3
Warm	4	3	1	2
Cold	4	2	1	3
Pain	4	1=	3	1=

Average rankings showing order of failure of numbered testing areas.

TABLE V.—ORDER OF SENSORY PARALYSIS IN REGIONAL ANÆSTHESIA

Reference	Number of Subjects	Number of Blocks	Agent	Nerves used	Order of sensory loss: Pain	Cold	Warm	Touch	Remarks
Goldscheider, 1886 ..	1	>2	Cocaine	Ulnar, Median	3=	1=	1=	3=	Pain returned first
Endres, 1929	2	8	Novocain Tutocaine	Ant. Cutaneous of thigh ; dorsal cutaneous of forearm	3=	1	2	3=	Spatial as well as temporal dissociation
Grundig, 1930 ..	9	9	Tutocaine	Ant. Cutaneous of thigh					Cold before warm
Heinbecker, Bishop and O'Leary, 1934 ..	3	3	Procaine	Not specified	3	1	2	4	Trained subjects
Dawkins, 1945 ..	?	?	Procaine	Extradural spinal blocks					Pain and temperature before touch
Kellgren and McGowan, 1948	1	?	Procaine	Ulnar					Dissociation of skin pain and "deep" pain
Merrington and Nathan, 1949	2	Several	Procaine	Median	1	2=	2=	4	Incidental observations

TABLE VI.—ORDER OF SENSORY PARALYSIS IN SPINAL ANÆSTHESIA

Reference	Number of Subjects	Number of Blocks	Agent	Order of sensory loss: Pain	Cold	Warm	Touch	Remarks
Bier, 1899	1	1	Cocaine					Pain before touch : temperature indefinite
Baglioni and Pilotti, 1909 ..	34	34	Stovain	1	2	3	4	
Thole, 1912	?	>3	Stovain	1	2	3	4	
Heinbecker, Bishop and O'Leary, 1932	3	3	Procaine	3	1=	1=	4	Untrained subjects
Heinbecker, Bishop and O'Leary, 1934	6	6	Procaine	3	1	2	4	Untrained subjects
Sarnoff and Arrowood, 1946, 1947*a* and *b*, 1948*a* and *b* ..	?	Several	Dilute Procaine					Pain before temperature and touch. Pricking pain before other types (1948*b*)

TABLE VII.—ORDER OF SENSORY PARALYSIS IN LOCAL ANÆSTHESIA

Reference	Number of Subjects	Number of Blocks	Agent	Method	Order of sensory loss: Pain	Cold	Warm	Touch	Remarks
Donaldson, 1885 ..	?	?	Cocaine	Instilled into eye					Pain before temperature
Shore, 1892	1	?	Cocaine	Painted on tongue					Pain before touch
Ponzo, 1909	?	?	Stovain	Skin injection	2	1	3=	3=	
Winkler, 1909	?	?	Cocaine	Cataphoresis					Pain before touch
Schilder, 1913	1	1	Stovain	Injection					Pain and cold before warm and touch
Hacker, 1914	>2	>12	Cocaine Novocain	Injection Cataphoresis Paint	1	2	3=	3=	Spatial dissociation observed. Exactly simlar results with many other substances, including hyper- and hypotonic saline
Felix and v. Frey, 1923	?	?	Novocain	Cataphoresis	1	2	?	?	
Goldscheider and Hahn, 1924	?	?	Cocaine Stovain, etc.	Injection					Cold before warm
Rein, 1924	?	12	Cocaine Stovain	Cataphoresis	1	2	3	4	"Burning" caused by hot stimuli persists after loss of touch
Schriever, 1928 ..	?	?	Cocaine	Cataphoresis					Dissociation between two types of cutaneous pain
Lewis, 1937	?	?	Cocaine	Cataphoresis					Pain before touch

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THE CHEMISTRY OF CEREBRAL CYSTS

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EARLIER work on the chemical analysis of the fluid in cysts found in some cerebral tumours centred around protein and some inorganic elements such as potassium, sodium and calcium (Stern, 1939; Cumings, 1944). Some estimations, however, were made of nucleoprotein and phospholipoid and from these results I postulated that some cysts might be the result of breakdown of tumour and brain tissues. Since then other investigations have been made in an attempt firstly to obtain evidence to support or refute this suggestion, and secondly to see if it were possible to determine the nature of the tumour by chemical methods.

MATERIAL AND METHODS

Fluids from 69 cases of cerebral cysts have been investigated, the majority having been obtained at operation, but a few were collected at autopsy, although this did not appear in any way to affect the results, most probably because the post-mortem was carried out only a few hours after death, during which time the body had been in the refrigerator. The tumour was classified histologically in 52 cases, in 6 a diagnosis of glioma only was made on biopsy, and in the other cases there was no histological evidence of tumour. This paper is devoted to the group of 52 cases in which the exact histological diagnosis was available.

The substances examined with the methods employed are as follows:

Cholesterol and alkaline phosphatase (King, 1946, very slightly modified), total protein and albumen—some by the methanol method of Pillemer and Hutchinson (1945) and some colorimetrically using the technique of Greenberg (1929) but using 26 per cent sodium sulphate (Majoor, 1947), hæmobilirubin (Harrison, 1947), muco-protein (Winzler *et al.*, 1948), amino-acid nitrogen (Hawk, Oser and Summerson, 1947), and deoxyribonucleic acid and ribonucleic acid adopting the procedure that Davidson *et al.*, 1948, used for bone-marrow tissue.

RESULTS

The three tables show the amounts of these substances found in the 52 cyst fluids. It will be seen that it has sometimes only been possible to estimate some of these substances owing to the varying quantity of material available.

The reasons for choosing these particular examinations require some few comments. It was thought necessary to know the protein levels in the fluids both from practical and theoretical considerations. The levels of cholesterol and alkaline phosphatase were expected to be a possible indication of the amount of fluid diffused from the blood, for it was

considered that they would be lower than the blood levels, although present in appreciable amount. Moreover, the amounts of alkaline phosphatase and hæmobilirubin would be a guide to the degree of hæmorrhage that had occurred during the formation of the cyst. It might be mentioned here that in a small series of cerebrospinal fluids personally examined none of these last three substances was found in any estimable quantity ; yet, in pleural and ascitic fluid, cholesterol and alkaline phosphatase were found in a concentration much the same as that found in hæmangioblastoma (*see* Table II), but in each case at a lower concentration than in blood.

Muco-protein was estimated as Winzler *et al.* (1948) had suggested that there was an increase of this substance in the blood of persons suffering from malignant tumours, and it seemed possible that, if this were true, a knowledge of the content of muco-protein in cerebral cysts might be of diagnostic value.

Amino-acid nitrogen was estimated as it was thought that its concentration in the cyst fluid might parallel that in the blood, or, if increased, then it would indicate a degree of protein degradation. It was thought possible that this would be seen in the more malignant or necrotic tumours.

Many of the cyst fluids have also been examined by partition chromatography using the paper strip technique (Consden *et al.*, 1944, and Dent, 1946), and, although some of the cysts from varying tumours have yielded differing results, yet no absolutely characteristic amino acids have as yet been demonstrated by this method.

It was suggested in my previous paper that the presence of nucleic acid was evidence of tumour breakdown. It is now known that the nuclear chromatin material contains deoxyribonucleic acid whilst the cytoplasm of cells contains ribonucleic acid. It was thought possible that cysts from malignant tumours might contain more, and innocent tumours less, deoxyribonucleic acid than ribonucleic acid, as more differentiated cells are known to contain relatively more ribonucleic acid. It is of interest that serum contains small quantities of each type of nucleic acid with rather more ribonucleic acid than deoxyribonucleic acid. It was found in a small series of sera that the amounts present of each are half to two-thirds of those found in most tumour cysts.

Considering the results seen in Table I it is apparent that the cholesterol figures in all except two fluids—one from a neurofibroma, and the other from an ependymoma—are lower than are found in blood, and that the alkaline phosphatase figures are all lower. Taken as a whole the total protein is low even though a few reach as high as 6 grammes per cent. It is interesting that in a number of fluids the percentage of albumen to the total protein is lower than would be seen in normal blood but this might be partly explained by a breakdown of albumen with a corresponding increase in amino-acid nitrogen, which in almost all cases is higher than the normal figure for blood serum. There is

practically no evidence of red cell destruction following a hæmorrhage as the hæmobilirubin content is low in all except one case. Muco-protein figures are relatively high for the astrocytomatous group but low for all other cysts. The pattern of the nucleic acids shows a higher ribonucleic acid than deoxyribonucleic acid although none of the amounts present is much higher than that found in a corresponding quantity of serum.

TABLE I

Name	*Choles.*	*Alk. phosph.*	*T.P.*	*Alb.*	*V.d.B.*	*Muco-prot.*	*Amino N*	*Deoxy*	*Ribo*	*Type of tumour*
Sch.	30	3·0	2·73	1·0						Astrocytoma
Har.	105	5·0	5·12							,,
Adl.	84		3·6							,,
Tay.	137	0	4·0	2·2	0·25					,,
Smi.	100	5·6	4·48	2·83		5·4	6·3	0·58	0·48	,,
Pre.	84	6·4	4·48	3·45	0·1	7·0	5·6	1·3	1·35	,,
Hal.	140		6·4	3·46		6·6	4·75			,,
Pat.	110	3·0	4·48	2·92	0·1	5·0	4·9	0·86	1·18	,,
Jen.	110		3·65			6·8	5·66			,,
Osb.	130	1·0	2·97	1·74	V.sl. tr.	3·5	6·9	0·75	1·0	,,
God.	113	1·0	3·7	2·55						Ependymoma
Oll.	240	1·6	1·56	1·2	1·25	2·85	8·34	0·28	0·4	,,
Bur.	140	6·0	6·2	3·61	0·4	4·4	7·75	1·5	1·55	Oligodendroglioma
Bur. 6/12 later	132	11·4	5·18	2·04	0·35	3·51	7·54	0·95	0·65	,,
Wal.	102	4·0	6·3	3·7	0·1	3·72	6·8	0·43	1·08	,,
Woo.	100		2·2							Neurofibroma
Wal.	280	6·0	3·7	2·0	0·2	3·2	6·2	0·175	0·55	,,
Abe.	170	3·2	5·31	3·06	<0·1	2·55	7·68	0·8	1·06	,,
Lan.	49	5·0	1·3							Endothelioma
Sam.	72	0	1·5	1·08	0·01					,,
Wak.	72	1·0	3·5		0·6					,,
Hol.	140	4·0	4·8	3·3	0·8	6·0	9·2			,,

Choles. = Cholesterol in mg.%

Alk. phosph. = Alkaline phosphatase in units

T.P. = Total protein in g.%

Alb. = Albumen in g.%

V.d.B. = Hæmobilirubin in mg.%

Muco-prot. = Muco-protein as tyrosine equivalent in mg.%

Amino N = Amino-acid nitrogen in mg.%

Deoxy = Deoxyribonucleic acid estimated as phosphate in γ per ml.

Ribo = Ribonucleic acid estimated as phosphate in γ per ml.

Some of the constituents examined in pituitary cysts as shown in Table II do show characteristic features. The cholesterol content is relatively high and the amino-acid nitrogen and muco-protein contents are distinctly higher than in blood. Alkaline phosphatase is low but some of the protein figures are surprisingly high.

TABLE II

Name	Choles.	Alk. phosph.	T.P.	Alb.	V.d.B	Muco-prot.	Amino N	Deoxy	Ribo	Type of tumour
Gil.	356		6·4			7·6	13·2	1·5	1·7	Pituitary cyst
Bod.	170	4·0	1·2	0·78						Cholesteatoma
Dow.	620		4·45							Craniopharyngioma
Mil.	150	1·9	5·25	3·0		6·4	14·0	1·12	1·24	,,
Kar.	102	13·0	2·76	0·71						,,
Mil.	40	2·4	2·8	1·53	0·1			0·66	0·55	Hæmangioblastoma
Isl.	50	1·5	1·31	0·83		2·0	3·13	0·46	0·43	,,
Wic.	65	2·0	3·32	1·69	tr.	5·07	5·25	0·85	0·8	,,
Sho.	66	0·4	3·33	2·01	<0·1	2·7	4·96	0·6	0·9	,,
Gal.	20	10·8	4·67	3·3	0·1	9·0	7·4	0·86	1·02	Hæmangioendothelioma
She.	105	9·9	6·7	2·5	0·1	10·4	9·5	1·0	1·0	,,

Choles. = Cholesterol in mg.%

Alk. Phosph. = Alkaline phosphatase in units

T.P. = Total protein in g.%

Alb. = Albumen in g.%

V.d.B. = Hæmobilirubin in mg.%

Muco-prot. = Muco-protein as tyrosine equivalent in mg.%

Amino N = Amino-acid nitrogen in mg.%

Deoxy = Deoxyribonucleic acid estimated as phosphate in γ per ml.

Ribo = Ribonucleic acid estimated as phosphate in γ per ml.

The 6 blood-vessel tumours with cystic formation are extremely interesting. There are 4 cerebellar cysts with hæmangioblastomatous nodules in the wall, and these are small tumours in relation to the size of the cyst. The amounts of the substances obtained are lower than in any other cyst, and are of the general order that one might expect from diffusion of fluid from blood vessels; in fact, they are similar to other fluids so formed, such as the pleural and peritoneal effusions which I have examined. It would seem highly probable that diffusion of fluid from the blood produces these cysts, and the low nucleic acid content, similar to that seen in serum, is further proof of this fact, and is evidence against any gross degenerative lesion. The closely allied tumour, the hæmangio-endothelioma, of which 2 examples are shown, occurring outside the cerebellum and having a relatively large tumour with small cysts, shows a quite different picture. Here the alkaline phosphatase, protein, muco-protein and amino-acid nitrogen are all relatively high, and these last two substances are higher than in blood serum. This last finding, as will be seen later, occurs in the more malignant tumours, and this, I believe, is histologically true with tumours of the hæmangio-endotheliomatous type.

The results in Table 3 show the figures obtained in the cysts from really malignant tumours. It can be said that in general all substances

TABLE III

Name	Choles.	Alk. phosph.	T.P.	Alb.	V.d.B.	Muco-prot.	Amino N	Deoxy	Ribo	Type of tumour
Fea.	98	9·0	2·47	1·57			9·2	0·69	1·15	Glioblastoma
Sta.	110	4·5	3·7	2·2	0·25	5·1	8·8	0·25	0·2	,,
But.	170		4·8		0·1	5·8	9·0	4·6	2·1	,,
Whe.			5·76				9·1	1·4	1·05	,,
Phi.	160	4·2	5·88	3·55	0·25	3·32	5·8	1·02	1·2	,,
Swa.	240	4·0	5·76		0·5	5·2	11·7	1·11	1·01	,,
Web.	142	3·8	5·37	3·5	0·2	1·5	7·0	4·72	1·14	,,
Sca.	163	3·6	6·78	3·5	<0·1	2·16	8·5	5·12	1·2	,,
Phi.	152	12·1	5·8	3·98	<0·1	3·9	9·6	1·0	1·02	,,
Pfe.	193		6·9					1·32	1·37	,,
Spa.		2·8	2·75		0·25		7·04			,,
Coo.	165	12·0	5·12	4·65	0·1	8·0	20·2	1·06	0·82	,,
Jam.	154	5·8	5·44	2·87	0·75	2·1	26·4	0·71	0·7	,,
Sle.	102	0·4	4·81	3·06						Sec. carcinoma-bronchial
Ske.	104	3·8	4·07	2·1	0·15	12·0	14·4	1·5	1·07	Sec. bronchial
Ric.	98	9·2	3·54	1·75	0·3	10·0	10·6	0·87	0·67	,,
Lai.	170	82·0	7·7	4·03	0·6	11·2	9·7	3·0	1·6	Sec. columnar
Kem.	426	41·4	8·83	4·25	1·2	2·16	12·0	0·7	1·25	,,
Nor.	122	4·0	6·27	2·82	<0·1	1·53	6·4	5·0	1·38	Sec. melanoma

Choles. = Cholesterol in mg.%

Alk. Phosph. = Alkaline phosphatase in units

T.P. = Total protein in g.%

Alb. = Albumen in g.%

V.d.B. = Hæmobilirubin in mg.%

Muco-prot. = Muco-protein as tyrosine equivalent in mg.%

Amino N = Amino-acid nitrogen in mg.%

Deoxy = Deoxyribonucleic acid estimated as phosphate in γ per ml.

Ribo = Ribonucleic acid estimated as phosphate in γ per ml.

are in greater amount than in any other type of cyst. The gliob'astomatous cysts show no evidence of gross hæmorrhage as indicated by the low hæmobilirubin content. The protein levels are high, yet the amino-acid nitrogen figures are higher than in serum or in any other cyst apart from those in carcinomatous deposits. Cholesterol is high but the alkaline phosphatase figures are not raised. Muco-protein figures are variable despite the malignant character of this type of tumour. The nucleic-acid pattern is frequently disturbed and in some cysts the figures for deoxyribonucleic acid are very considerably increased and are in excess of the ribonucleic acid, even though these are also raised.

The 6 cysts from secondary deposits of carcinoma show striking features. Protein is high, but the amino-acid nitrogen is very considerably raised. Muco-protein in some is very considerably increased, whilst some high figures for deoxyribonucleic acid are also recorded. There is one very interesting feature, namely, the high alkaline phospha-

tase seen in the cases of columnar-cell carcinoma. These are the highest figures seen in any type of cyst, and in neither tumour would the primary appear to be in the intestine, nor in either was there any obvious blood contamination.

Discussion

Fluid from cerebral cysts is almost always obtainable only when the tumour and cyst are of such a size as to give rise to clinical manifestations, and this is most likely to be some months after the cyst first begins to form. The interpretation of the results of the examination of the fluid at this late stage, therefore, presents difficulties, and it may be quite impossible to express an opinion as to whether the breakdown of the tumour through a poor blood supply or from enzymatic action was or was not the initiating cause. However, the results shown in the case of the hæmangioblastomatous cysts do suggest that the fluid in these cases represents such as would be found following the passage of fluid from the blood. Here there is no evidence of hæmorrhage nor is the nucleic acid pattern different from that which is seen in serum. This is also true of the cysts found in association with neurofibromata except that here the cholesterol level is raised, but this substance may be derived from the tumour cells. All other cysts show alterations in their composition from this picture, and also from the type of fluid seen in the pleural cavity when this fluid is a simple transudate. A high protein level in a cyst fluid cannot be taken as a clear indication of an increased exudate from the blood unless the other substances present are also in proportion to those in the blood, and this is quite often not the case. Higher figures for cholesterol would seem to indicate breakdown of tumour or of brain, and when these are seen in conjunction with an amino-acid nitrogen and muco-protein level above that of blood, it would appear to be strong evidence in favour of necrosis. Further, the general pattern of nucleic acid distribution is such as would lead one to suppose that there was increased cellular destruction. The results shown in cysts other than those in hæmangioblastoma and neurofibroma do, in fact, support the view that necrosis of tumour has occurred, even though at some later stage some blood constituents may have been added. The more malignant tumours are seen to give evidence of necrosis to a greater degree than the more innocent growths. It is no uncommon occurrence for histologists to find degenerate changes in tumours in close association with cysts, and, frequently, evidence is found of some small degree of hæmorrhage even though, chemically, this series shows little evidence of any degree of hæmorrhage having taken place.

It is when consideration is given to the question of chemical analysis being of assistance in diagnosis that an even greater difficulty arises. It does not seem to be possible to state that any type of cyst has an absolutely characteristic chemical pattern. Even so, it is possible to

indicate some features that may be of assistance in diagnosis. A very high cholesterol figure suggests a pituitary cyst, while a very considerably raised alkaline phosphatase has occurred only in some cases of secondary carcinoma. A malignant and, to a lesser degree, a necrotic tumour are characterized by the presence of a high amino-acid nitrogen, a high protein and a raised deoxyribonucleic acid content. It should also be possible to distinguish between the two types of hæmangiomatous tumour, for, in that commonly seen in the cerebellum, all substances which have been examined have been found to be in low concentration.

SUMMARY

The chemical analysis of 52 cyst fluids from cerebral tumours are recorded and discussed.

The results suggest that degeneration of tumour initiates the formation of cerebral cysts followed by some transudation of fluid from blood vessels, except for those cysts found in association with hæmangioblastoma and neurofibroma in which no evidence of necrosis is found. The possible diagnostic value of the examinations performed are mentioned, especially as they relate to cysts in conjunction with malignant tumours.

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THE ADVANCE OF FUNCTIONAL RECOVERY AFTER RADIAL NERVE LESIONS IN MAN

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THE war reawakened interest in the rate of functional recovery after various types of nerve injury. The problem is a practical one for, without some knowledge of this rate, rational treatment and prognosis are impossible. For example, time and experience have shown that radial palsies associated with closed fractures of the humerus should be treated conservatively at first, as the majority of these cases recover spontaneously; if recovery does not occur within a certain period, surgical intervention is then indicated. The whole management of such a case must be based on estimates of the expected times of functional recovery. Apart from such clinical applications, the investigations have been useful because they have drawn attention to some of the features of the process of restoration of function after severance of a nerve.

During the past ten years, the problem has been investigated clinically and experimentally. The rate of growth of axon tips after crush and suture of the sciatic nerve in the rabbit has been investigated by Medawar and Young (1940) and Gutmann, Guttmann, Medawar and Young (1942). At an appropriate time after the lesion in each individual, the nerve was exposed, mobilized and crushed with fine forceps at millimetre intervals, working from the periphery towards the lesion. The first point at which a reflex response was obtained under light anæsthesia was found to contain fine axons when examined histologically; these were the tips of the most rapidly advancing axons. By this method the rate of advance of these tips was found to be 3·5 mm./day after a suture and 4·4 mm./day after crushing the nerve. These investigators also studied the rate of advance of signs of motor and sensory recovery in the rabbit. The rates were found to be significantly smaller than the rates of advance of the axon tips as measured by the above method. By comparing the times of motor recovery after high and low lesions of motor nerves, apparent rates of advance of 3·1 mm./day after nerve crushing and 2·0 mm./day after suture were found. Similar methods applied to sensory recovery gave rates of 2·1 mm./day and 1·6 mm./day over the distances available

in the rabbit. None of the results showed signs that the fibres did not "advance down the nerve at a constant rate"; later work has shown however, that over the greater distances and times found in man, the rates may decline.

This experimental work has brought out the fact that the different methods available do not all measure a single rate of regeneration. The advance of the axon tips is a relatively simple process but, before functional recovery can occur, there must be a certain degree of maturation of the new nerve fibres by increase in diameter and medullation, and, probably, also maturation of the new end-organs and reversal of atrophic changes. It is now known that the maturation is controlled by the peripheral connexions and this introduces a further complication into considerations of the apparent rate of regeneration. A still further complication is that the degree of maturation necessary for function probably varies not only between different muscle groups (Aitken, Sharman and Young, 1947) but also with the level and distance of the muscle from the lesion.

Instead of the apparently simple notion of rate of regeneration of new nerve fibres, the experimental work has therefore shown that we have to consider the probability that different apparent rates of regeneration will be recorded by various methods of study and with various nerve lesions in Man.

The opportunities for the measurement of the rate of outgrowth of axon tips in Man are necessarily limited. There is good evidence that this rate does not differ markedly from that in the rabbit (Seddon, Medawar and Smith, 1943; Bowden and Gutmann, 1945). Tinel's sign may be regarded as the clinical equivalent of the method of pinching the nerve used by Medawar and Young. Seddon *et al.* (1943) considered that this sign was unsatisfactory since its advance was erratic in all cases apart from sutures. However, the whole question of the significance of Tinel's sign has been recently examined again by Napier (1949) who finds the sign consistent with Sunderland's observation that the rate of its advance decreases steadily.

The problem of the time course of the advance of functional recovery in Man presents further difficulties which have been discussed by Young (1942) and Gutmann and others (1942). Seddon *et al.* (1943) found that a straight line fitted the data in some of their cases but, in others, such a regression line implied that recovery commenced before the injury had been inflicted. These workers pointed out the manifest absurdity of such a situation and therefore fitted curves to the data; as a result, they found a decrease of the rate of recovery of function with the passage of time. However, they felt that the rates of recovery might be reasonably assumed to be constant over moderate ranges of time and distance.

Sunderland (1947) has made a critical analysis of much of this work; objections were raised to the methods employed in these experiments, especially to the "assumption . . . that the rate (of advance) is constant."

The most serious criticism levelled at the work of Seddon and his colleagues is that their calculations were made from unreliable and inadequate anatomical data. Sunderland and his collaborators have collected more human anatomical data on which greater reliance may be placed and have calculated various rates of recovery (Sunderland, 1946, 1947; Sunderland and Hughes, 1946*a*, 1946*b*; Sunderland and Ray, 1946).

In this work Sunderland attempted to determine " the rate of advance of functionally mature motor fibres " by considering the time taken for the recovery of two muscles whose shortest distance " from a point on the nerve proximal to the site of origin of its first branch " had been measured. The rate of advance was taken as the ratio of the difference between these distances and the difference between the times. This calculation was repeated for successive segments of the nerve and a set of rates obtained. Various assumptions are implicit in this method and these will be discussed later. It may be noted immediately that, while a constant " rate of advance " is not assumed for the whole nerve, this rate is assumed to be constant over the successive segments of the nerve of varying lengths.

In our view, it is preferable to avoid a consideration of rates of recovery and rather to consider only the lapse of time between the injury or suture and the first sign of the recovery of voluntary activity in the different muscles. It has therefore seemed useful to make another investigation of the problem using Sunderland's anatomical data and a different statistical approach. The aims of this survey are to see if it is possible to obtain more precise knowledge of the time course of recovery after various lesions of the radial nerve in Man. Particular attention has been paid to apparent time of onset of the process of functional recovery, the effect of the type and level of the lesion (cf. Stopford, 1920) and the effect of delay and length of resection upon the rate of recovery after suture. An attempt has also been made to see whether the final degree of recovery was related to the advance of the appearance of recovery.

Material.—The histories and follow-up records of all the radial nerve injuries treated at the Oxford Nerve Injury Centre were examined. Owing to the difficulties of obtaining complete records of clinical cases, especially where repeated examinations were required, many cases had to be discarded. For this investigation, follow-up examinations were made at intervals of one to two weeks according to circumstances. The minimum requirements were considered to be knowledge of the level of the lesion and complete records of the times at which voluntary contractions were first found in the different muscles. Clearly, only those cases in which some recovery of all, or almost all, the muscles normally supplied by the radial nerve, could be observed were suitable for this enquiry. In the cases of sutures, the interval between injury and operation and the length of resection had to be known. A final assessment of recovery was made and information was sought about type and duration of physiotherapy. Only cases of complete lesions which fulfilled these requirements were admitted for analysis. The methods of clinical examination have been described by Seddon (1947). The level of the lesion in relation to the lateral epicondyle was found as accurately as possible by inspection of wounds, X-rays in

closed fractures, and by palpation of the neuroma. Where nerves were explored or sutured, direct measurements were taken. A fair proportion of cases was followed systematically by a single observer, but all examiners had received similar training and methods were standardized as far as possible. The time at which the first sign of movement in each muscle was detectable was recorded. The M.R.C. rating of voluntary power was used; if more than a flicker of movement was present, the observation was discarded for the purpose of this study since it was assumed that voluntary contractions must have appeared some considerable time before that particular examination.

In our series of cases we were left with 17 cases of suture, only one of which made a complete recovery, and 14 cases of lesions in continuity and of the latter, 5 made a perfect recovery of motor function as judged by routine clinical methods. For brevity we shall refer to the distance of the lesion or the lines of suture from the lateral epicondyle as the "level of lesions"; if these are above this point they will be considered positive and, if below, negative. The interval between the time of injury and suture will be called "delay." Since the level of the lesion is known it will be possible to calculate the distance from the lesion or suture to each muscle showing recovery by using the anatomical data in each case. The data are summarized in Tables I and II.

TABLE I.—CASES OF SUTURE OF THE RADIAL NERVE

Case	*Age (years)*	*Type of injury*	*Level of suture above lateral epicondyle (cm.)*	*Delay before operation (days)*	*Length of resection (cm.)*	*Distance from suture to most distal muscle showing recovery (cm.)*	*Galvanism*	*Final recovery*	
R7	18	Laceration	− 3·0	74	4·0	11	0	M5	S3
R55	25	G.S.W.*	+ 2·4	57	6·3	19	+	M3+	S2
O8	31	Compound sepsis*	+ 3·0	235	4·7	20	+	M4	S3
A59	20	G.S.W.*	+ 4·0	129	6·0	21	+	M4	
B77 30	30	G.S.W.*	+ 8·5	127	3·0	25	+	M4	S3
M8	27	G.S.W.*	+ 9·0	307	3·0	25	+	M4	S2
F26A	22	G.S.W.*	+10·0	263	5·7	27	+	M2	S3
T39	30	Compound*	+10·0	161	2·7	26	+	M2	S2
H53	23	G.S.W.	+11·0	293	3·5	28	±	M4	S2
G47	26	G.S.W.*	+12·0	231	3·2	29	+	M4	S3
B63	41	Compound*	+12·0	283	1·5	29	0	M3	S3
B145	31	G.S.W.	+14·0	70	2·2	31	+	M4	S3
L41	29	G.S.W.	+14·5	223	5·3	31	+	M4	S4
J(TA)	21	G.S.W.*	+15·0	188	2·5	32	+	M3	S3
F2	25	G.S.W.*	+17·0	377	7·0	34	0	M4	
P35	21	G.S.W.* Brachial art. severed	+18·0	217	3·0	35	+	M3	S3
B84	27	G.S.W.	+20·6	192	3·7	38	±	M4	S3

*Fracture of humerus.

±Intermittent

TABLE II.—RADIAL NERVE LESIONS IN CONTINUITY

Case	Age (years)	Type of injury	Level of lesion above lateral epicondyle (cm.)	Distance from lesion to most distal muscle showing recovery (cm.)	Galvanism	Final recovery	
A22	21	G.S.W.	+ 4	21		M5	S4
L10	25	Fracture	+10	27	0	M5	S4
H81	21	Fracture	+12	29	+	M5	
E19	23	Strep. polyneuritis ..	+18	35	+	M5	
B1	63	Dislocation of shoulder..	+36	51	0	M5	S3
P20	36	Fracture	+12	29	0	M4	S2
P11	30	Fracture	+12	26	0	M4	S2
H110	33	G.S.W. and fracture ..	+14	31	+	M4	S3*
A10	20	G.S.W.	+15	31	+	M4	S2
B5	29	G.S.W. and fracture ..	+17	34		M3	S3
C118	22	G.S.W.	+20	37	0	M4	S2
J29	70	Dislocation of shoulder..	+29	46	+	M4	S4
P49	18	Traction	+30	47	+	M3	S4
M23	35	G.S.W.	+38	54	0	M4	S2

*Touch and prick normal, pressure gave rise to tingle.

METHOD OF ANALYSIS AND RESULTS

Sunderland gives figures for the levels at which branches of the nerve trunks enter the muscle bellies. These distances are measured along the course of the nerve trunks and are given in relation to the appropriate fixed bony landmarks. The data are based on the dissection of 20 specimens each of the radial, median, ulnar and sciatic nerves. Considerable variation was found and the range of this variability stated. The distances which we used have been based on this information.

We first consider the relationship between the distances from the site of injury of the first muscles to show recovery could be detected and the time after injury. These results are shown in Table III. When the distances of these muscles from the lesion are plotted against the respective times at which they recovered, the points are seen to be somewhat scattered but have a linear trend. Regression lines were fitted and the expected mean distances calculated for different times, namely 50, 100, 150, 200, 250 and 300 days; these means and the 95 per cent confidence limits for individual observations are shown in Table IV. The interpretation of these limits will be discussed later.

The next stage involved the investigation of the complete history of the individual cases. The distances from the lesion to successive muscles in which recovery occurred were plotted against the times elapsing between the date of injury or suture and the functional recovery of the

TABLE III.—DISTANCES AND TIMES FOR MUSCLES SHOWING FIRST VOLUNTARY RESPONSE (RADIAL NERVE)

Case	*Type*	*Distance from lesion (cm.)*	*Time after injury (days)*
A22	L.i.c.	4·5	86
L10	,,	10·5	81
P11	,,	10·2	145
P20	,,	10·2	121
P49	,,	12·0	209
H81	,,	12·5	81
A10	,,	13·2	125
B5	,,	15·2	194
E19	,,	16·2	128
C18	,,	18·2	147
B1	,,	20·5	174
M23	,,	26·0	122
J29	,,	27·2	211
R7	Suture	1·7	167
A59	,,	2·2	104
O8	,,	3·5	107
B77	,,	6·7	142
R55	,,	7·1	118
M8	,,	7·2	177
H53	,,	9·2	181
F26A	,,	10·5	264
T39	,,	10·5	303
G47	,,	12·5	151
B63	,,	12·5	307
J(TA)	,,	13·2	162
B145	,,	14·5	145
L41	,,	15·0	161
F2	,,	15·2	308
P35	,,	18·5	198
B84	,,	21·1	201

TABLE IV.—MEAN VALUES AND CONFIDENCE LIMITS FOR INDIVIDUAL OBSERVATIONS OF THE DISTANCES OF PROXIMAL MUSCLES SHOWING RECOVERY OF VOLUNTARY ACTIVITY AT DIFFERENT TIMES

	Lesions in continuity			*Sutures*		
Time after injury (days)	*Mean value (cm.)*	*Lower conf. limit*	*Upper conf. limit*	*Mean value (cm.)*	*Lower conf. limit*	*Upper conf. limit*
50	8·8	0	22·3	7·1	0	18·2
100	12·3	0	25·8	8·5	0	19·6
150	16·2	2·7	29·6	9·9	0	21·0
200	19·3	5·8	32·8	11·3	0	22·4
250	22·8	9·3	36·3	12·7	1·6	23·8
300	—	—	—	14·1	3·0	25·2

individual muscles; these plots were made for each patient. Three diagrams are given with the relevant clinical data in figs. 1 and 2.

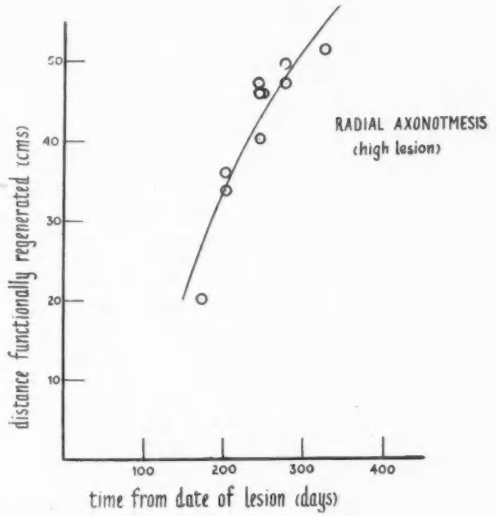

FIG. 1.—Case record and graph to illustrate the progress of a patient with a high lesion in continuity.

Case BI., male, aged 63.

12.12.40 : Dislocation of right shoulder, musculospiral palsy, lesion 36 cm. above the lateral epicondyle. No galvanism.

Date of first voluntary contraction	*Muscle*	*Time since injury (days)*	*Distance from lesion to muscle (cm.)*
5.6.41	Lat. head triceps ..	174	20·5
7.7.41	Br.	206	33·7
	E.C.R.L. ..		36·0
18.8.41	E.C.R.B. ..	248	40·2
	E.C.D.		45·7
	E.C.U.		45·7
	E.M.D.		47·2
22.9.41	A.P.L.	283	46·9
	E.P.L.		49·4
11.11.41	E.P.B.	332	51·4

28.4.42 Recovery had reached grade M5 S3.

It is clear that the points follow a well-known trend where the slope is steep at the beginning and gradually decreases. Moreover, although the trends of the different cases show the same general pattern, there is very great variation in the rate of the change of the slope. It appears to us, therefore, that at present any attempt to state an estimate of average growth rate is, at the best, very misleading.

It appeared more satisfactory to fit a curve to the data of each case and to use the equations of these curves as means of interpolation to

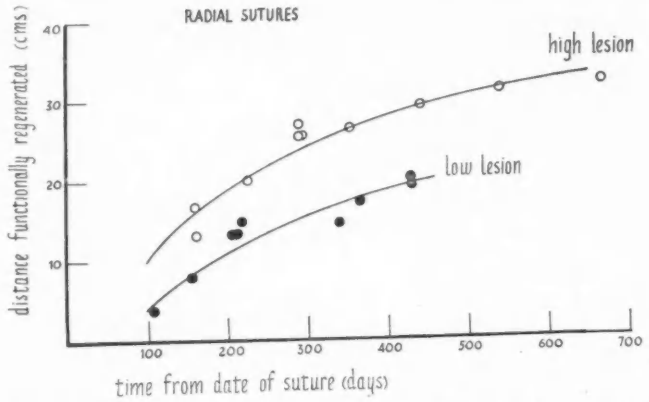

FIG. 2.—Case records and graphs illustrating the progress of two patients with high and low lesions respectively in which the radial nerve was sutured.

Case O8, male, aged 33.

23.12.41 : Compound fracture, Right humerus. Moderate sepsis.

2.9.42 : Suture of nerves 3 cm. above lateral epicondyle.
Delay in repair 235 days.
Length of resection 4·7 cm.
Galvanism thrice weekly.

Date of first voluntary contraction	*Muscle*	*Time since injury (days)*	*Distance from suture to muscle (cm.)*
18.12.42	E.C.R.L. ..	107	3·5
5.2.43	E.C.R.B. ..	156	7·7
26.3.43	E.C.U.	205	13·2
2.4.43	E.C.D.	212	13·2
9.4.43	E.M.D.	219	14·7
6.8.43	A.P.L.	338	14·4
3.9.43	E.P.L.	366	16·9
8.11.43	E.P.B.	432	18·9
	E.1.		19·9

14.4.47 Recovery had reached stage M4 S3.

Case J(TA), aged 21.

22.9.43 : Gunshot wound of left arm with fractured humerus.
Radial nerve palsy, lesion in continuity.

29.3.44 : Suture of nerve 15 cm. above lateral epicondyle.
Delay in repair 188 days.
Length of resection 2·5 cm.
Galvanism thrice weekly.

Date of first voluntary contraction	*Muscle*	*Time since injury (days)*	*Distance from suture to muscle (cm.)*
7.9.44	Br. ..	162	13·2
	E.C.R.L. ..		15·5
9.11.44	E.C.R.B. ..	225	19·7
11.1.45	E.C.D.	288	25·2
	E.C.U.		25·2
	E.M.D.		26·7
15.3.45	A.P.L.	351	26·4
14.6.45	E.P.L.	442	28·9
20.9.45	E.P.B.	540	30·9
24.1.46	E.I.	666	31·9

23.5.46. Recovery reached grade M3 S3.

A.P.L.	Abductor pollicis longus.
Br.	Brachio-radialis.
E.C.D.	Extensor digitorum communis.
E.C.R.B.	Extensor carpi radialis brevis.
E.C.R.L.	Extensor carpi radialis longus.
E.C.U.	Extensor carpi ulnaris.
E.I.	Extensor indicis.
E.M.D.	Extensor digiti minimi
E.P.B.	Extensor pollicis brevis.
E.P.L.	Extensor pollicis longus.

find estimates of distances regenerated at certain times, 100, 150, 200, 250 and 300 days for each case. This method allows comparison of the cases with a minimum of assumptions.

Examination of the plotted points suggested that the slope varies inversely with the time over the range considered. Consequently the curve $y = a + b \log t$. was fitted where y denotes the distance (cm.) from the lesion or suture to the most distal muscle showing recovery at time t days after the lesion or suture. The estimates of the parameters a and b were found by the method of maximum likelihood, which, in this case, reduces to the method of least squares.

It must be emphasized that we use these curves in a purely descriptive manner; no hypotheses are made as to the interpretation to be placed on the parameters a and b nor are their values used save as a method of interpolation. This is an extremely simple type of curve and its flexibility in fitting a wide variety of data makes it particularly suitable for our purpose. The extent to which it may be considered a "true" growth curve will not be considered here, since this problem would demand a discussion of the physiology of growth and its possible mathematical representation.

Figs. 1 and 2 show three examples of this curve fitted to the data; these cases were picked at random for the purpose of illustration. It is clear that these curves will cut the horizontal axis to the right of the origin; the distance between the origin and this intersection is a measure of the time elapsing between the injury or suture and the apparent beginning of the process of recovery of voluntary activity. We have called this the initial period, and clearly, knowledge of its duration under varying

conditions would be of great interest. We have estimated its length from the fitted curves; values for the different lengths of this period will be found in Table V.

TABLE V.—ESTIMATES OF DISTANCES RECOVERED AT VARIOUS LEVELS AND OF THE PARAMETERS OF THE CURVE $y = a + b \log t$
DMR—Distal Muscle Recovered

Type	Case	Level above lateral epicondyle (cm.)	Estimated initial period (days)	Estimated distance (cm.) recovered after t days					Parameter estimates	
				100	150	200	250	300	a	b
L.i.c.	A22	4	72·7	7·4	16·9	23·7	DMR	DMR	−100·28	53·87
	L10	10	56·5	13·0	22·2	28·8	DMR	DMR	− 91·96	52·48
	H81	12	74·8	7·2	17·1	DMR	DMR	DMR	−105·94	56·55
	E19	18	73·5	11·0	25·6	35·9	DMR	DMR	−154·05	82·54
	B1	36	100·0	—	18·9	32·4	42·8	51·4	−215·67	107·80
	P11	12	83·4	4·2	13·5	20·1	25·3	29·5	−101·83	53·00
	P20	12	51·6	8·8	14·2	18·0	21·0	23·4	− 52·52	30·67
	H110	14	76·6	6·8	17·2	24·6	30·3	34·9	−110·99	58·91
	A10	15	68·9	7·8	16·4	22·4	27·1	30·9	− 88·95	48·39
	B5	17	57·8	8·2	14·3	18·7	22·0	24·8	− 61·18	34·71
	C118	20	75·7	7·2	17·6	24·9	30·6	35·3	−110·91	59·03
	J29	29	50·6	13·5	21·6	27·3	31·7	35·3	− 77·77	45·64
	P49	30	127·4	0	4·7	12·8	19·2	24·4	−137·78	65·46
	M23	38	41·5	23·3	34·1	41·7	47·6	52·5	− 98·76	61·05
Suture	R7	−3	146·1	0	0·6	6·7	11·5	DMR	−107·03	49·44
	R55	2	57·1	6·9	12·0	15·5	18·3	DMR	− 50·04	28·49
	O8	3	66·6	4·2	8·4	11·3	13·6	15·5	− 43·31	23·75
	A59	4	76·6	3·2	8·0	11·4	14·1	16·2	− 51·45	27·32
	B77	8·5	106·5	0	9·8	18·1	24·5	DMR	−133·94	66·07
	M8	9	134·3	0	3·4	12·1	18·8	24·3	−148·17	69·63
	F26A	10	98·2	0·3	6·1	10·2	13·4	16·0	− 65·70	32·98
	T39	10	148·6	0	0·2	6·4	11·1	15·0	−107·06	49·29
	H53	11	119·3	0	6·2	14·0	20·0	25·0	−129·55	62·38
	G47	12	85·2	3·9	13·9	21·0	26·5	30·6	−109·41	56·68
	B63	12	234·0	0	0	0	3·6	13·6	−299·71	126·49
	B145	14	42·8	11·9	17·6	21·6	24·8	27·3	− 52·66	32·29
	L41	15	110·9	0	11·7	22·7	31·3	DMR	−181·30	88·67
	J(TA)	15	45·7	9·9	15·2	18·8	21·7	24·0	− 48·76	29·37
	F2	17	193·0	0	0	1·3	9·6	16·4	−195·69	85·62
	P35	18	75·9	5·8	14·3	20·4	25·1	28·9	− 91·19	48·50
	D84	21	103·1	0	12·2	21·5	28·8	34·7	−150·44	74·73

It has seemed worth while to attempt to compare the initial periods for cases where the wounds are of the same nature. In our series there are 5 cases of gunshot wounds where the nerves showed lesions in continuity and were treated conservatively and 13 cases where the nerves were sutured. For the lesions in continuity, the mean initial period was 64 days with a standard error of 6 days; for the sutures, the

corresponding mean is 96 days with a standard error of 11 days. Further investigation shows that the variances of the two groups differ significantly ($F = 7{\cdot}98$, $f_1 = 13$, $f_2 = 4$). This result indicates that the in tial progress of the cases treated conservatively is more uniform than that of those sutured.

The means of two samples cannot be compared by the usual t-test if the samples are drawn from populations with differing variances. To overcome this difficulty we have used Scheffe's (1943) method ; this gives a value of $t = 1{\cdot}81$ ($f = 4$). Such a value is just below the 90 per cent level and we consider that in an experiment of this type the difference between the mean initial periods of these groups must be considered real, in the sense that it is not entirely attributable to sampling errors. This result is in agreement with the conclusions of Gutmann and Guttmann (1942) that the initial delay is longer in those cases where the nerve had been sutured. It may be noted that the delay period of these authors is defined essentially in the same manner as the initial period considered in this paper.

While this method deals with some of the earlier phases of recovery, it gives no information as to the process as a whole. Another approach involves a consideration of the distances at which voluntary activity could be observed at different times, e.g. 100 days, 150 days, etc., after the lesion. In a laboratory experiment it would be possible to make such observations at precise times ; this is not the case with a clinical experiment and we have to be satisfied with the best estimates that can be found from the data.

Table V gives the estimates of the distances at which voluntary activity was observable 100, 150, 200, 250 and 300 days after the injury or suture. The levels of the injury, the estimated initial periods and the parameters of the curve for the different cases are also tabulated. Some of the cases show no signs of voluntary activity 100 days after the injury, while in other cases the most distal muscle of the limb has recovered its function 250 days after the injury. It will be seen that the levels of the injuries range from 3 cm. below to 38 cm. above on the lateral epicondyle.

It is clear that these distances may depend on many factors, e.g. the nature of the injury, the delay before operation and the length of nerve resected ; some factors, such as the degree of retrograde degenerat on, cannot be measured in clinical cases and there are certainly factors operating about which we are ignorant. We shall consider some of the factors which may affect the distances recovered at different times ; our choice is limited not only by our knowledge but also by the available data.

When the value of some variable, e.g. distance recovered, is thought to be dependent upon a number of factors, one may investigate the extent to which the factors influence the dependent variable by the method of multiple regression.

This method was used to consider three of the possible factors that may influence the distance recovered at different times after the injury

or suture, namely : level of lesion, delay before operation and length of nerve resected. In the suture cases all three may be operative, while only the first can be considered in cases of lesions in continuity. The analysis showed that these factors considered individually had no effect on the distance recovered at different times but their joint effect is not negligible.

The effect of the height of the lesion alone cou'd be investigated for all cases. The effect appears to increase with the time but since the significance level is not higher than 93 per cent, it is clear that a larger number of cases must be analysed before a definite conclusion can be reached.

Finally, an effort was made to establish some connexion between the treatments, the different factors which have been measured, and the degree of recovery. One result is clear ; out of 14 cases of lesions in continuity, 5 showed complete motor recovery by routine clinical testing whereas only 1 of the 17 suture cases showed this result. If we attempt to extend this result and, for example, try to relate the degree of recovery to the level of the lesion, by means of some kind of contingency table, we find that the numbers of cases with the same characteristics are too small to enable reliable conclusions to be established.

Discussion

(1) *Time of appearance of recovery.*—One of the greatest problems of the clinician in dealing with nerve injuries may be to know when he should explore the lesion and when he may reasonably expect some signs of recovery. It must be borne in mind that the clinician is dealing with the rate of advance of functional recovery and this differs from the rate of outgrowth of the tips of the axons.

Knowledge of the delay that might be expected before signs of voluntary activity are shown in the muscle nearest to the lesion would be of great value. The length of this period cannot be stated precisely, but it should be possible to find upper and lower limits between which the delay might be reasonably expected to lie. Such limits are known as confidence limits and it is clear that the narrower these limits, the greater their value. The times elapsing between the date of injury and the appearance of voluntary activity in the nearest muscle for our series are given in Table III. The means alone give no guidance as to the results to be expected for an individual ; for the consideration of a particular case we must use confidence limits.

The application of these confidence limits may be illustrated for example by case C18. The patient had been treated conservatively and at 150 days after the injury we find (Table IV) that the confidence limits are 2·7 and 29·6 cm. ; these figures mean that it would not be unusual if the distance of the recovered muscle were only 2·7 cm. nor, indeed, if one 29·6 cm. away were functioning normally. If at 250 days a muscle 5 cm. from the lesion had not recovered then, possibly, surgical interference might be indicated.

It is clear from Table IV that the distances showing functional recovery are greater in the cases of lesions in continuity. Nevertheless, the confidence limits are wide and cannot be improved until more records are available for analysis.

(2) *Initial period.*—Examination of the curves fitted to the observations (e.g. figs. 1 and 2) shows that none of them passes through the origin and the distance of the intersection of the curve and the horizontal axis from the origin enables us to make an estimate of the length of an "initial period." It is necessary to be very careful as to the meaning of this period.

Earlier workers have shown that the problem of recovery of motor function is a complex one, for, in addition to the actual advance of the axon tips, all the processes leading to functional completion must take place. The problem was critically discussed by Young (1942), and it is relevant to consider it once more. Three broad phases may be distinguished; these are, an "initial delay," the period of advance of the axon tips from the lesion to the end-organ and lastly, a "terminal delay."

The initial delay in the sense used by Young differs from the initial period considered in this paper and refers to the delay before the axon tips reach the distal segment of the damaged nerve. The initial period here calculated includes the initial delay in Young's sense and also the time taken for the axon tips to reach the end-organs and all the processes included by Young in the "terminal delay."

Functional connexion must be formed between the axons and the end-organs; the nerve fibres must reach a certain diameter and degree of myelinization before they are capable of transmitting impulses of the appropriate speed and frequency. The process of maturation is itself dependent upon the state of the end-organ. Furthermore, the atrophic changes in the end-organ probably have to undergo some degree of reversal and patterns of neuromuscular activity have to be re-established and possibly readjusted. We are ignorant of the time course of maturation, of the degree necessary for the restoration of function and of the critical degree of atrophy. Evidently, the initial period, giving a measure of all of these processes, is of great interest.

(3) *Rate of advance of regeneration.*—It might be argued that it is still possible to calculate some kind of "average growth rate" which would be useful to the clinician.

Sunderland (1947) has discussed this point in his review of previous work and has attempted to solve the problem by calculating average rates for distal and proximal segments of nerve. The method of this author depends on certain assumptions, for example,

(1) In any one segment of nerve there is no difference in the rate for fibres destined for two muscles and this rate does not diminish over the distance from the first to the second muscle.

(2) The delay at the site of injury is the same for fibres destined for the two muscles. On theoretical grounds this would only appear

to be true if there were no disruption of the supporting tissue of the nerve, as in a lesion in continuity.

(3) In the two muscles there is no significant difference in the delay between the arrival of the nerve fibres and return to function.

It would seem that although the calculations were made over several short segments, the fundamental objections, some of which Sunderland himself has raised, remain ; the first assumption is especially questionable. Since the rate of advance of recovered muscles declines it is, in principle, impossible to specify a simple rate. It is, however, permissible to calculate, for each case, the distance recovered at any time after injury or suture.

Examination of Table II shows that in the 5 cases that recovered completely the advance of restoration of function was more rapid than in the other lesions in continuity at comparable levels. In addition to being more rapid, these were the only cases in which complete motor recovery, as judged by clinical testing, was found. There was presumptive evidence that each case showed a practically straightforward lesion in continuity. Sensory recovery was incomplete in B1 ; in H81 and E19 there is no reliable assessment of sensory recovery. In the single low suture that made a complete motor recovery the process was not completed 250 days after suture.

These considerations suggest that there may be some relationship between the rate of advance of restoration of function and the treatment that has been followed, i.e. the injury has been treated conservatively or by suture. However, it appears that a successful secondary suture of a nerve may lead to results as satisfactory as those found with the more extensive lesions in continuity which were not operated upon. This is not unexpected since in all but cases of pure axonotmesis, there is a varying amount of intraneural scar. This fact suggests that the category " lesion in continuity " contains various types, some of which involved rather slight lesions, others, more serious and including intraneural damage, might perhaps have done better if treated surgically.

(4) *Level of lesion.*—The regression analysis indicated that no matter what the nature of the original lesion, whether sutured or a lesion in continuity, or what the degree of recovery, the level of the lesion has an effect on the length of nerve which recovers in a given time and this effect increases with the passage of time. It is of interest to note that more than twenty-five years ago Stopford (1920) concluded that the level of the lesion influenced the recovery of function.

(5) *Length of resection.*—In a preliminary report to the Medical Research Council, Zachary gave figures for the critical lengths of resect on of human nerves. These figures have been published by Seddon (1948) for the human radial nerve ; the critical lengths are 7·5 cm. (high and intermed ate levels with transposition) and 5·3 cm. (all levels without anterior transposition). In our cases all resections were less than 7·5 cm. and only four exceeded 5·3 cm. (Table I). Every case was immobilized in a plaster cast for three weeks after operation, the elbow flexed in the

position for satisfactory suture. The joint was then gradually and slowly extended over a period of about five weeks by means of a Turnbuckle screw.

This investigation has indicated that we can only as yet distinguish the broad form of the pattern of the time course of motor recovery. The rate of advance of appearance of recovery of voluntary activity falls off with the time elapsing after the injury and with the distance recovered; there is an apparent initial period during which there is no detectable evidence of the process of recovery. There are wide variations between the times of appearance of recovery of individuals, suggesting that there are numerous factors in operation. It would be tedious and rather futile to attempt to list all these factors, but leaving aside the variability of individuals, we think of the varying traumata following injuries, the variation of the extent of the nerve injury, variations in the extent and density of the intra- and extra-neural scar tissue and the difficulties of establishing functional connexions between nerve fibres and end-organs which may themselves have undergone adverse changes as a result of denervation.

The data presented here and the subsequent analyses have made some of the difficulties manifest, but are, unfortunately, insufficient to solve the problems involved.

Conclusions and Summary

(1) 17 cases of suture and 14 cases of lesions in continuity of the radial nerve in man are examined. All the cases of the series showed signs of recovery in all the muscles normally supplied by the nerve.

(2) One case of suture showed complete motor recovery whereas five of the lesions in continuity showed complete motor recovery.

(3) Using Sunderland's anatomical data, the distances between the suture or lesion and the muscles supplied by the radial nerve were calculated and plotted against the respective times taken for recovery

(4) The pattern of the plotted points indicted that the process of advance of appearance of recovery of function could be fitted by a curve of decreasing slope and curves of the form $y = a + b \log t$ proved to fit the points well in all cases. This means that the rate of advance of recovery from muscle to muscle is at first high and then declines.

(5) The initial period elapsing before the apparent beginning of the process of voluntary activity can be observed is of more uniform length for lesions in continuity than for sutures. The mean initial period for lesions in continuity being 64 ± 6 days and that for sutures, 96 ± 11 days.

(7) The expected distances over which voluntary activity occurred after 100, 150, 200, 250 and 300 days were calculated for individual cases and are given in Table V.

(8) Confidence limits for the distance expected to show recovery of voluntary activity in the first proximal muscle at given times are shown in Table IV.

(9) The advance of appearance of voluntary activity was most rapid in those cases of lesions in continuity that ultimately made a complete motor recovery.

(10) The level of the lesion affects the distance that recovers in a given time, its effects increasing with the time after suture or injury. There are strong indications that the rate of advance of appearance of voluntary activity in otherwise comparable cases increases with the level of the lesion.

(11) The length of the delay before operation and the length of resection have no apparent effect on the distance showing recovery of voluntary activity after a given time. It must be noted that the delay was less than 200 days in more than half the cases and in only one case was it more than 300 days.

We wish to thank Professor H. J. Seddon for the use of the case notes and Professor J. Z. Young for the valuable criticism and advice which have been continually at our disposal.

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THE VALIDITY OF THE CONCEPT OF MULTIPLICITY OF REPRESENTATION IN THE MOTOR CORTEX UNDER CONDITIONS OF THRESHOLD STIMULATION[1]

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In the first paper of this series [1] it was shown that suprathreshold stimulation of the motor cortex induced movements involving several muscles rather than one muscle only. Since these movements frequently involved more than one of the large somatotopic areas (face, arm and leg) the experiments suggested the existence of an extensive overlap in the motor cortex in various species including monkey. It was believed that these results were not explainable on the basis of physical spread and it was shown that they persisted even on stimulation of a small cortical area after it had been surgically isolated from the remainder of the cortex. On this basis and also, as the result of experiments with near threshold stimuli [2, 3, 4], it was believed that the organization of the motor cortex cannot be represented by a cortical mosaic with different, sharply delimited foci for different muscles but rather seems to involve extensive overlaps of groups of specific cortical neurons which on stimulation activate groups of muscles in a definite temporal and spatial sequence (principle of multiplicity of cortical representation of movements). Since the chief claim of the adherents of the mosaic theories of cortical representation lies in the observation of isolated muscle responses under conditions of threshold stimulation a study was made of the response of the limbs by means of multiple electromyograms on excitation of the motor cortex with threshold stimuli.

All experiments were performed on *Macacus rhesus* monkeys anæsthetized with 0·45 to 0·5 c.c. of dial-urethane. After exposure of the brain, various parts of the motor cortex were stimulated by means of condenser discharges (Goodwin stimulator) through mono- or bipolar silver electrodes, the latter with an interelectrodal distance of 2 mm. EMGs were recorded through fine copper wires sewn into the muscles (cf. previous papers). The threshold was determined by either varying the frequency or the intensity of the stimulus. The duration of the individual impulse was 7·4 ms.

[1]Aided in part by the Office of Naval Research.

Results

Figs. 1 and 2[1] were obtained from stimulation of the same site (3 mm. from the middle line and about 1 mm. anterior to the central fissure). The monkey lay in a prone position on a table with the right hindleg

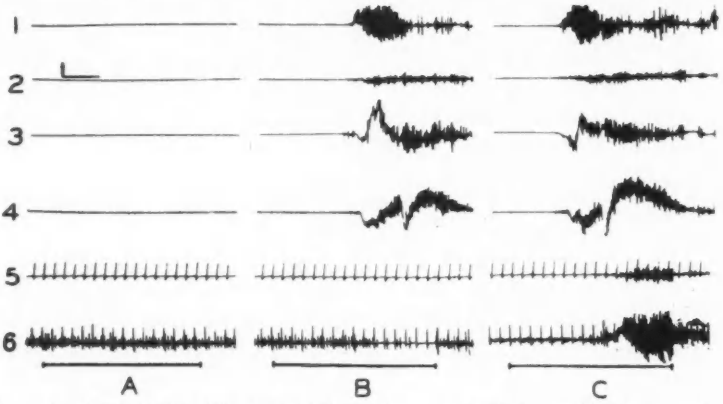

Fig. 1.—Stimulation (Horizontal line above each letter indicates onset and duration of stimulation) of a site in the " leg area of area 4 " (3 mm. lateral to the mid-line and immediately anterior to the central fissure) with condenser discharges of 2·5 V (A), 2·8 V (B) and 3·0 V (C). Frequency of stimulation 90/sec., duration of impulse 7·7 ms. Calibration 100 microvolts (vertical line) and 1 second. (horizontal line) 1, Hamstrings; 2, Quadriceps ; 3, Tibialis ; 4, Gastrocnemius ; 5, Biceps ; 6, Triceps.

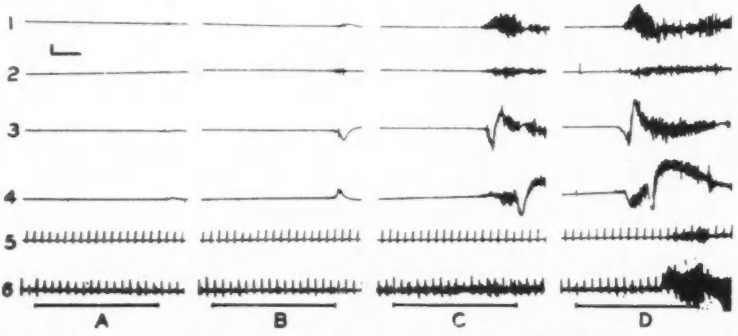

Fig. 2.—Same site, muscles and calibration as in fig. 1. Stimulation 3 V and the following frequencies/sec. : 21 (A), 26 (B), 32 (C), 90 (D).

extending laterally. The knee and ankle showed an angle of 100 degrees and 120 degrees respectively and were " free."[2] Fig. 1 shows the effect of increased voltage at a given frequency while fig. 2 illustrates the effect of increasing frequency at a given voltage. In both cases the conditions

[1]The regular potentials in Nos. 5 and 6 are due to the EKG.

[2]This term is used in contradistinction to fixation of a joint at a certain angle.

were so chosen that with either procedure a gradual transition from subthreshold to suprathreshold excitation was accomplished. At an intensity of 2·5 V no effect appeared (A) while with a slight increase in intensity (2·8 V) a distinct electromyogram was noted in all recorded hindleg muscles. Apparently, there is no evidence for "discrete" response here even when a threshold stimulus is used provided that the occurrence of a contraction is based on objective recordings rather than visual observations. It is interesting to note that this threshold stimulation leads also to an effect in the triceps muscle whose tonic activity is abolished in the second half of the stimulation period. With a further slight increase in voltage (3 V, fig. 1, C) there is no essential change in activity of the recorded hindleg muscles but a distinct contraction of the triceps occurs which is accompanied by a slight co-contraction in the biceps.

A very similar reaction is obtained from the same point on changing the frequency of stimulation while the intensity is kept at 3 V (fig. 2). There is no response to a stimulus of 21/sec., a very brief and minute reaction at the end of the stimulation period to a stimulus of 26/sec., and a distinct reaction in response to a frequency of 32/sec. Here again, there is no evidence of a "discrete" response, the various hindleg muscles showing the same threshold. With a further increase in frequency to 90/sec. a contraction appears in the triceps with a slight co-contraction in the biceps. Comparison of fig. 1 C with 2 D shows the complete reversibility of these reactions. Both figures illustrate also that with increasing stimulation, either by increased frequency or increased voltage, the summation period decreases. Here again the hindleg muscles act as one group and the foreleg muscles as another, the summation period of the former being shorter but there is no difference in the summation time between the hindleg muscles such as hamstrings and the anterior tibial muscle.

Fig. 3 shows a similar experiment on the effect of increased frequency

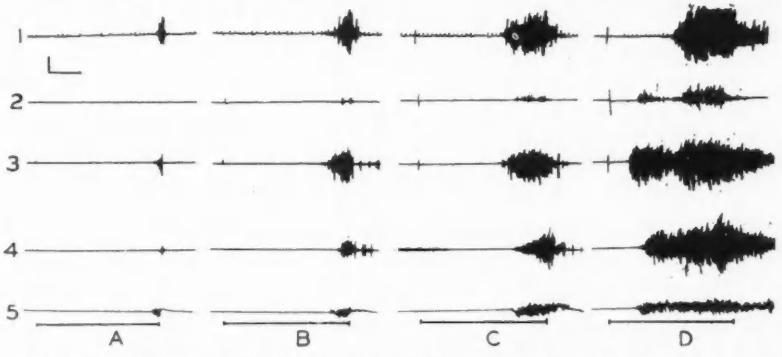

FIG. 3.—Stimulation of a site in the leg area of area 4 with 4·2 V and frequencies/sec.: 33 (A), 42 (B), 53 (C), 83 (D). Calibration 300 microvolts and 1 second. Knee and ankle were fixated at 160 degrees and 170 degrees respectively. 1, Flexor digitorum communis; 2, Gastrocnemius; 3, Tibialis; 4, Flexor part of biceps femoris; 5, Gracilis.

while the leg was fixated in extension (knee 160 degrees, ankle 170 degrees). Minute reactions occur at the threshold (fig. 3 A) in 4 recorded muscles. They increase in intensity and show a decrease in summation time as the frequency of stimulation is augmented. The gastrocnemius shows some activity only in conjunction with stronger contractions of the tibialis in agreement with our earlier interpretation that the contraction of the gastrocnemius is a co-contraction. Similar findings were made for the arm areas.

Fig. 4 shows the effect of increasing voltage on a point in the biceps part of area 4 while the arm is " free.".[1] It is interesting to note that at

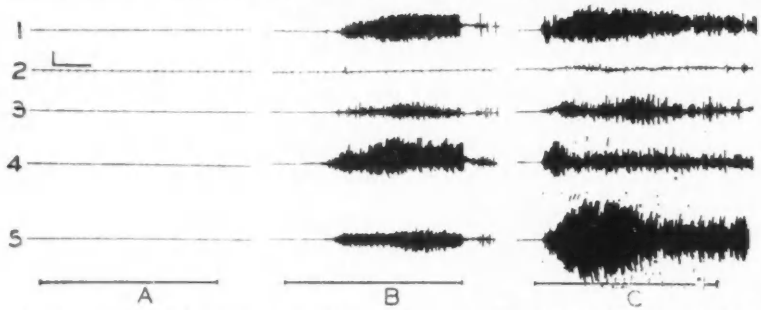

FIG. 4.—Stimulation in the lateral arm area of area 4 with 1·5 V (A), 1·9 V (B) and 2·9 V (C). Frequency 90/sec. Calibration 300 microvolts and 1 second. 1, Biceps; 2, Triceps; 3, Flexor carpi; 4, Extensor carpi; 5, Brachioradialis.

1·9 V four muscles show distinct activity which do not react at 1·5 V and that also contractions appear in the face area at 1·9 V but not at 1·5 V. With further increase in intensity there is as expected an increase in amplitude and a decrease in summation time in the EMG of these four muscles but little qualitative change is seen. Only a trace of activity appears in the triceps which is thought to be a co-contraction.

Finally, an example is presented of the response of foreleg muscles under conditions of fixation (fig. 5). In this experiment a site 13 mm.

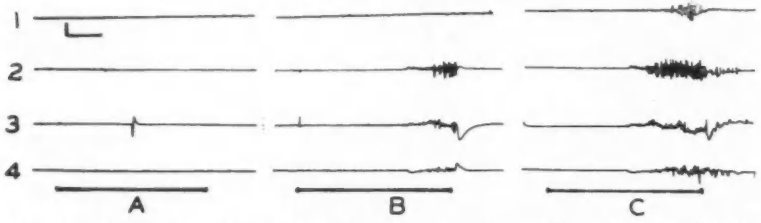

FIG. 5.—Stimulation of a point in the biphasic (Triceps-Biceps) zone of area 4. Frequency 83/sec., intensity 2·1 V (A), 2·3 V (B) and 2·8 V (C). Calibration 100 microvolts and 1 second. Elbow fixated at 170 degrees. 1, Triceps; 2, Biceps; 3, Flexor carpi ulnaris; 4, Extensor carpi ulnaris.

[1]Shoulder retracted (60 degrees), elbow 90 degrees, hand on table in pronation.

lateral from the mid-line and just anterior to the central fissure is stimulated. This point, located in the zone of overlap existing between the biceps and triceps sites, on stimulation gives rise primarily to a contraction of the triceps complex[1] when the elbow is fixated at 45 degrees. However, fixation of the elbow in extension favours the response of the biceps through proprioceptive facilitation (fig. 5). Consequently, under threshold conditions (B) a response in biceps and wrist muscles appears and only upon increasing intensity (C) does a contraction occur also in the triceps.

In agreement herewith it is seen in this figure that the summation time is shorter for biceps than for triceps under these special proprioceptive conditions. The experiments show that the multiple response is characteristic for threshold reaction with and without fixation of the leg. However, proprioceptive impulses may definitely affect the threshold of a muscle or group of muscles.

Experiments of this type were performed in areas 4, 6 and also in that part of the postcentral gyrus which is immediately adjacent to the central fissure. An example of the latter group is shown in fig. 6 which

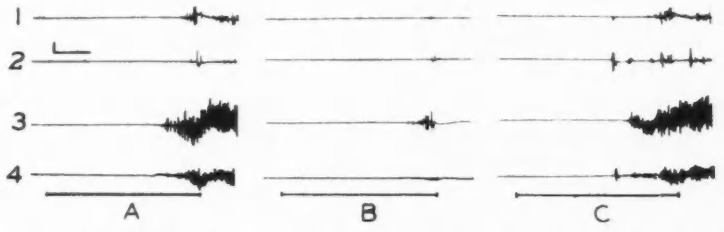

FIG. 6.—Stimulation of the postcentral gyrus immediately posterior to the central fissure. Leg not fixated, knee 100 degrees, ankle 120 degrees. Intensity 1·9 V, frequency/sec. 32 in A and C and 26 in B. 1, Hamstrings; 2, Quadriceps; 3, Tibialis; 4, Gastrocnemius.

illustrates again the complete reversibility of these effects. To give a more complete survey than can be shown conveniently in figures with EMG records Tables I and II are reproduced which give several examples concerning the appearance of activity in muscles with increasing intensity of stimulation. These tables show that in various parts of the motor cortex the threshold reaction is multiple and not confined to a single muscle or part of a muscle.

The experiments presented in this paper establish the fact that even under conditions of threshold stimulation the muscle response is multiple and appears in form of activity in functionally related muscle groups which were described in some detail in earlier papers. The multiplicity of representation of movements and not the mosaic of sharply defined foci of muscles or parts of muscles seems to underlie the organization

[1]Triceps and flexor carpi (*see* [3]).

TABLE I.—ACTIVITY IN VARIOUS MUSCLES ON CORTICAL STIMULATION WITH NEAR THRESHOLD STIMULI

			Area 4											
			1	2	3	4	5	6	7	8	9	10	11	12
Expt	*Volt*	*Freq*	*Ha*	*Tib*	*Ga*	*Sol*	*Lu*	*Bra*	*Quad*	*Per*	*Tri*	*Bi*	*EC*	*FC*
6	2·3	83									0	*	(*)	(*)
	2·3	83									***	*	*	*
	2·6	83									***	*	*	*
7	1·5	90						0			0	0	0	0
	1·9	90						0			0	0	0	0
	2·3	90						***			(*)	**	***	***
	3·3	90						***			(*)	**	***	***
13	1·9	90	0	0	0	0			0		0			
	2·1	90	0	0	0	0			0		0			
	2·3	90	**	**	*	(*)			(*)		**			
15	1·9	90		0	0									
	2·1	90		0	0									
	2·3	90		***	*									
	3·3	90		***	(*)									
17	1·5	90	0	0	0		0			0				
	1·9	90	*	**	*		**			*				
	2·3	90	*	**	*		**			*				

1 Ha—Hamstrings
2 Tib—Tibialis
3 Ga—Gastrocnemius
4 Sol—Soleus
5 Lu—Lumbricalis
6 Bra—Brachioradialis
7 Quad—Quadriceps
8 Per—Peroneal
9 Tri—Triceps
10 Bi—Biceps
11 EC—Extensor carpi
12 FC—Flexor carpi

(*) = trace; * to **** indicate increasing amplitude of the EMG.

of the motor cortex even under conditions of threshold stimulation. The chief qualitative response observed on stimulation with increasing intensity of frequency is the appearance of co-contraction in the antagonists.

Also, in the area from which both foreleg and hindleg movements can be elicited the threshold of the neurons activating these two somatotopic areas is different and depends on the site of stimulation. Either the hindleg or foreleg muscles contract at threshold but in either case the threshold contraction is not confined to a single muscle but to those functional muscle groups (biceps complex, etc.) which were described in our earlier papers. Furthermore, the threshold in the biphasic (biceps-triceps area) is modifiable through proprioceptive factors (cf. also fig. 5) but no matter whether biceps or triceps shows the lower threshold the EMGs reveal a multiple response on threshold stimulation. Finally, these results were confirmed in experiments in which frequency and

TABLE II

No.	*Volt*	*Freq*	*Ha*	*Tib*	*Ga*	*Sol*	*Quad*	*Per*	*Tri*	*Bi*	*Bra*	*FC*	*EC*
						Area 6							
4	1·9	90								(*)			(*)
	2·3	90							0	*	*	(*)	*
	3·3	90							0	*	*	(*)	*
	4·8	90							(*)	**	**	**	**
11	2·6	90	0	0	0	0	0						
	2·9	90	*	(*)	(*)								
	3·3	90	**	**	*	0	*						
16	2·9	90								0	0	0	0
	4·0	90								0	0	0	0
	5·5	90								***	(*)	(*)	*
19	2·9		(*)	(*)	(*)		0						
	3·3		**	*	(*)		(*)						
	4·0		****	**	*		(*)						
	4·8		****	**	*		(*)						
20	3·3		(*)	0	0	0	0		0				
	4·0		*	0	0	0	0		0				
	4·8		**	**	0	0	*		(*)				
	6·3		****	****	0	**	**		***				
						Area 3							
18	1·5	90	0	0	0	0	0						
	1·6	90	0	0	0	0	0						
	1·7	90	*	**	(*)	0	**						
	1·9	90	**	***	*	*	***						
9	2·9	90							0	0	0	0	0
	4·8	90							0	0	0	0	0
	5·5	90							0	**	**	**	**
10	3·3	90							0	0	0	0	0
	4·0	90							*	**	*	(*)	*
	4·8	90							*	***	**	**	***

voltage were kept constant but the duration of the individual impulse was varied. With the use of square waves it was found that increase of duration of the impulse from 3 ms to 4 ms converted a subthreshold response into a threshold reaction and the latter was again multiple as indicated by the appearance of EMGs in several muscles. There is no evidence of a fundamental difference in the behaviour of areas 6 and 4 (and also that part of the postcentral gyrus adjacent to area 4) under these conditions. Our experiments support Walshe's criticism of the concept of " discreteness " as a characteristic function of area 4.

It appears to be not very probable that the muscles of the fingers thus far inadequately studied under our experimental conditions behave

differently in principle but the experiments ought to be extended to these muscles. It is also possible that if only single stimuli were applied to the cortex a more selective activity may appear in the striated muscles than was seen in our experiments. Such experiments are planned for the future but the validity of such experiments for the interpretation of physiological function of the motor cortex would be small indeed since voluntary movements even of the smallest degree are not the result of single but repeated impulses of varying frequencies (Lindsley and others).

Summary

Stimulation of the motor cortex in anæsthetized monkeys (*Macacus rhesus*) under threshold conditions caused by a gradual increase in frequency, voltage or duration of impulse shows that not single muscles or parts of muscles are activated but muscle groups which are functionally interrelated. Such grouped muscle activity which seems to be the basis of co-ordinated movements is induced in a similar manner from all parts of the motor cortex on threshold stimulation. No essential differences were found between areas 4 and 6 in this respect. The experiments appear to be incompatible with the mosaic concept of cortical organization even under conditions of threshold stimulation and give further support to the principle of multiplicity of representation of movements in the motor cortex as the basis for the execution of movements initiated voluntarily or by electrical stimulation of the motor cortex.

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THE SPECIFICITY OF THE ELECTROMYOGRAPHIC METHOD FOR THE INVESTIGATION OF THE MOTOR CORTEX [1]

BY

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DENNY-BROWN [1] pointed out recently that the electromyographic method may have serious limitations at least under conditions of voluntary innervation since physical spread may occur from active to nonactive units in the same muscle and also from active to inactive muscles of the same extremity. Since the electromyographic method has been used extensively in this laboratory for the study of functions of the motor cortex [2–10] and the spinal cord [11, 12] a critical evaluation of the specificity of this method appears to be important.

METHOD

The experiments were performed on monkeys anæsthetized with 0·45 c.c. dial-urethane. The motor cortex was exposed and stimulated with condenser discharges for five seconds. The activity of muscles of the contralateral extremities was recorded by means of Offner amplifiers and inkwriters through fine copper wires sewn into the muscles. The copper wires were insulated except for a few millimetres which were bared and buried in the muscle. The bare parts of these electrodes were separated by a distance of about 1 cm. In several experiments 3 to 4 pairs of electrodes were sewn into the biceps muscle in order to record from different portions of this muscle. The extremities were fixated as in previously reported experiments.

RESULTS

The purpose of the present paper is to present evidence that activity in one muscle does not cause a physical spread of current to an adjacent muscle under conditions of cortical stimulation and furthermore to demonstrate that, if only a part of a muscle shows activity while another part of the same muscle is at rest, the EMG records indicate adequately this result.

Fig. 1 shows part of a record in which a biceps point in area 4 was stimulated and the activity of 6 muscles was recorded in the contralateral forearm. The elbow was fixated at 150 degrees throughout the experiment. The triceps muscle showed no activity whereas the biceps, the extensor carpi ulnaris and radialis and the extensor digitorum communis and pro-

[1] Aided in part by the Office of Naval Research.

prius III, IV showed a distinct EMG. Part A of fig. 1 shows the record under control conditions whereas part B shows the effect of sectioning of the nerves supplying the extensor muscles of the fingers. It is clearly evident that the denervated muscles failed to show any activity following cortical stimulation while the normally innervated muscles showed the same activity as in part A. This record gives no evidence for a physical spread of activity from active to non-active adjacent muscles under conditions of cortical stimulation.

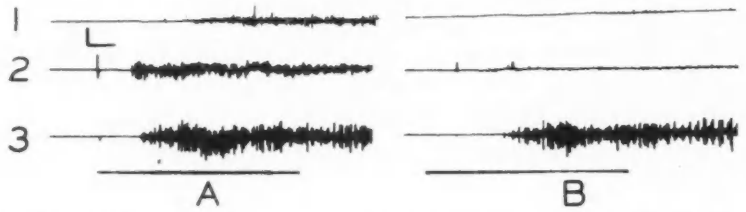

FIG. 1.—EMG records from extensor digitorum proprius III, IV (1), extensor digitorum communis (2) and extensor carpi radialis (3).[1] Stimulation of a biceps point in the contralateral area 4 with condenser discharges 4·2 V, 76/sec. Fixation of the elbow in extension (150 degrees). Calibration 100 microvolts (vertical line) and 1 second (horizontal line). Duration of stimulation indicated by horizontal lines below the record. A before, B after sectioning of nerve to the first two muscles.

Fig. 2 shows the influence of a gradual inactivation of a muscle in response to cortical stimulation and its effects on the EMG. In part A of fig. 2 it is seen that the activity of the flexor carpi ulnaris and extensor carpi ulnaris occurs in 2 phases alternating with one another. When the tendon of the extensor carpi ulnaris is cut the cortically induced activity is no longer reinforced by proprioceptive reflexes [7, 11] and the response in this muscle is greatly reduced while that of other muscles (cf. the EMG of the flexor carpi ulnaris, for example) is practically unchanged. Weakening of the response of the extensor carpi ulnaris is reflected also in more subtle changes. The second burst in the EMG of the extensor carpi ulnaris is no longer present in part B and consequently does not show its inhibitory action on the flexor carpi ulnaris (reciprocal innervation)[2] Finally, denervation of the extensor carpi ulnaris leads to specific elimination of its activity only.

The observation of Sherrington [14] that biceps femoris consists of two parts which are flexor and extensor in function offers an opportunity to study the specificity of the myographic method under these special conditions. If has been shown previously that fixation of a joint at different angles greatly increases the responsiveness of the muscle

[1]All experiments were performed on Rhesus monkeys. The records read from left to right.

[2]Reciprocal innervation has been shown to persist after deafferentation (Sherrington [13]). However, impulses originating in the contracting muscles seem to intensify reciprocal innervation phenomena.

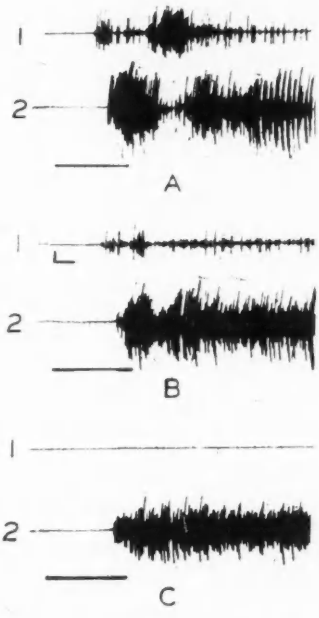

FIG. 2.—EMG records from extensor carpi ulnaris (1) and flexor carpi ulnaris (2) on cortical stimulation from area 4 with 4·7 V and 71/sec. Posture and calibration as in fig. 1. A, control; B after tenotomy; and C after denervation of the extensor carpi ulnaris.

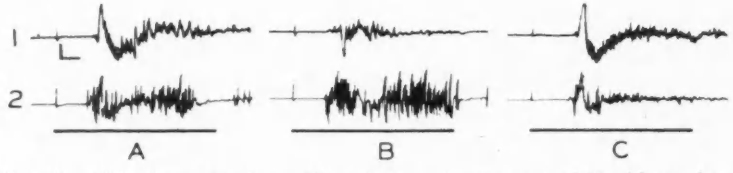

FIG. 3.—EMG from the flexor (1) and the extensor part of the biceps femoris (2) on cortical stimulation of area 4 with 4·2 V and 83/sec. In A and C knee and ankle are fixated at 160 degrees, in B at 70 degrees. Calibration 300 microvolts and 1 second.

which is stretched while that of the relaxed muscle is lessened to cortical or reflex stimulation. This principle was applied to the biceps femoris[1]. Fig. 3 shows that in A and C while knee and ankle are fixated at 160 degrees the flexor part of the biceps femoris shows the greater response than when these joints are fixated at 70 degrees. Conversely it is apparent from the records that the extensor fraction of this muscle responds optimally in the latter position (B).

Another example for the fact that the electromyographic method is

[1]We are indebted to Miss Jane Hyde for this experiment.

able to record adequately varying degrees of activity in different parts of the same muscle is given in fig. 4. In this experiment three pairs of electrodes were sewn into the biceps muscle in an attempt to record its activ ty from the medial, intermediate, and lateral parts separately while the record obtained from the flexor carpi ulnaris serves as an

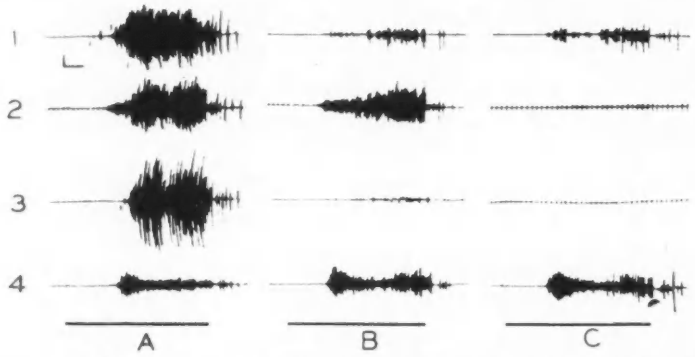

FIG. 4.—EMG from a lateral (1), intermediate (2) and medial (3) part of the biceps brachii and from the flexor ulnaris (4). Between A and B, and B and C some nerve branches supplying the biceps were sectioned. Calibration 100 microvolts and 1 second.

indicator of the constancy of the excitability of the motor cortex. This figure shows that the latter remains constant throughout the experiment in which the nerve supplying the biceps muscle was progressively divided. The elimination of part of the nerve fibres affects different sections of the biceps in an unequal degree. Thus, fig. 4, B shows that activity in the medial section (3) is almost eliminated while it is only slightly reduced in the adjacent part (2). Further sectioning of the nerve (between B, C) eliminates activity in the intermediate and medial part of the muscle while that of the lateral part (1) remains unchanged.

COMMENT

The experiments described in this paper show (1) that activity of a muscle may be accompanied by complete silence in the electromyographic record of an adjacent muscle; (2) that even in parts of the same muscle different degrees of activity may be recorded at the same time. The fact that nerve section to one particular muscle eliminates activity in this muscle although the activity of an adjacent muscle may be considerable proves that at least for studies involving stimulation of the motor cortex the electromyographic method as used in this laboratory is a reliable indicator of activity in individual muscles. Moreover, the electromyographic method may be used to show different degrees of activity in different parts of the same muscle. This could be demonstrated not only by specifically blocking out certain parts of a muscle through partial

section of the nerve supplying this muscle but also by alterations in posture (flexion or extension of the knee) whereby different parts of a muscle such as the biceps femoris was subjected to conditions which would favour proprioceptive reinforcement of a cortically induced movement in one part of the muscle only. The decrease in the responsiveness of a muscle as the result of tenotomy shown in this paper under conditions of stimulation of the motor cortex and previously in reflex studies [11] as well as its increased response when the tendon of the muscle is loaded [9, 12] furnish additional illustrations of the specificity of the electromyogram as an indicator of muscular activity. Since it is thus far the only method which allows a semi-quantitative insight into the muscular co-operation of an *intact* limb [3] the data presented in this paper should encourage its use in the study of muscular co-ordination under conditions of reflex and cortical stimulation.

SUMMARY

Experiments on the reliability of the electromyographic method under conditions of stimulation of the motor cortex are reported. In all experiments performed on anæsthetized monkeys (*Macacus rhesus*) pairs of fine copper wires bared for a few millimetres were sewn into six muscles of arm or leg. No evidence of spread of current from an active to a non-active muscle was found. A denervated muscle remains inactive although it may be surrounded by highly active muscles. If parts of a muscle are denervated the EMG potentials may be present in one part of a muscle and absent in another. Muscles such as the biceps femoris which consist of a flexor and extensor part can be shown to have different degrees of activity on cortical stimulation of a suitable focus in these two parts depending on the position of the knee. These experiments indicate that the electromyogram is a reliable indicator of activity in a muscle or part of a muscle induced by stimulation of the motor cortex. The experiments formerly published on spinal reflexes whose activity was estimated by EMG records likewise suggest the validity of the statements made above for reflex experiments.

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Notices of Recent Publications

Etudes Psychiatriques : Historique — Méthologie — Psychopathologie Générale. By Henri Ey. Desclée de Brouwer et Cie. Bibliothèque Neuropsychiatrique de Langue Française. Paris, 1948. Pp. 263. (Price unstated.)

The author's design is to articulate a framework for psychiatric thought which shall be neither exclusively mechanistic nor exclusively psychogenetic, and yet provide the possibility of a dynamic interpretation of mental illness. The thesis is developed along historical and largely philosophical lines, with extensive reference to French psychiatric literature. As the main representative of a school which favours psychogenetic dynamic principles, the work of Freud is also discussed at length.

The book suffers, for the British reader, by a certain remoteness from clinical medicine. If some of the quotations from other authors and discussions of their views could have been replaced by the presentation and discussion of actual cases, it would have been easier to understand the application in practice of the author's formulation. "Le dilemne mécano-psychiste" hardly finds a place in Anglo-American psychiatry. This may be partly because the psychophysical dualism to which it corresponds is to a large extent discredited both in philosophical and psychiatric circles ; but also because it is felt to be a dead issue, debate about which is not productive of further advance. Pragmatic as the attitude is, it has its justification in the fact that with every factual discovery a certain number of old-established problems are found to be due, either to the misuse of words, or to asking the wrong questions. Gilbert Ryle's recent work, "The Concept of Mind," shows how much the growth of psychological understanding has undermined the Cartesian position, against which Ey has to spend so much ammunition.

Psychological Aspects of Clinical Medicine. By Stephen Barton Hall. 1949. Pp. xii, 416. London : H. K. Lewis and Co. Price 21s.

This book is based on a course of lectures for postgraduate and Final Year students at Liverpool, and therefore for an audience with general medical interests. The author sensibly departs from the plan of the standard textbook of psychiatry, and gives a great amount of space and attention to the psychoneuroses, the physical repercussions of abnormal mental states, and the psychological symptoms which may accompany bodily illness. Nevertheless the plan adopted is not entirely well conceived, and there are many subjects, extremely important to the general practitioner, which are touched on in only the most cursory way. Practically no guidance is given on the early diagnosis of schizophrenia, and the discussion of the symptomatic psychoses, of the mental disorders of the puerperium, and those associated with arteriopathic disease, are much too short and casual. If one should expect of a textbook that it should give more space to ascertained fact than to matters of speculation, one senses a lack of proportion. Nevertheless on the subjects to which the author gives the main emphasis, his presentation is balanced and far from extreme, and should be found helpful by those for whom the book is intended.